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Kindling of Life Stress in Bipolar Disorder: Comparison of Sensitization and Autonomy Models

Rachel B. Weiss,
McLean Hospital/Harvard Medical School

Jonathan P. Stange,
Department of Psychology, Temple University

Elaine M. Boland,
Department of Psychology, Temple University

Shimrit K. Black,
VA Boston Healthcare System/Boston University School of Medicine

Denise R. LaBelle,
Department of Psychology, Temple University

Lyn Y. Abramson, and
Department of Psychology, University of Wisconsin-Madison

Lauren B. Alloy
Department of Psychology, Temple University

Abstract

Research on life stress in bipolar disorder largely fails to account for the possibility of a dynamic relationship between psychosocial stress and episode initiation. The kindling hypothesis (Post, 1992) states that over the course of recurrent affective disorders, there is a weakening temporal relationship between major life stress and episode initiation that could reflect either a progressive sensitization or progressive autonomy to life stress. The present study involved a comprehensive and precise examination of the kindling hypothesis in 102 participants with bipolar II disorder that allowed for a direct comparison of sensitization and autonomy models. Polarity-specific tests were conducted across the continuum of event severity with respect to both impact and frequency of life events. Hypotheses were polarity- and event-valence specific and were based on the stress sensitization model. Results were only partially consistent with the sensitization model: individuals with more prior mood episodes had an increased frequency of minor negative events prior to depression, and of minor positive events prior to hypomania. However, the number of past episodes did not moderate relationships between life events and time until prospective onset of mood episodes. These results are more consistent with a sensitization than an autonomy model, but several predictions of the sensitization model were not supported. Methodological strengths, limitations, and implications are discussed regarding putative changes in stress reactivity that may occur with repeated exposure to mood episodes in bipolar II disorder.

Corresponding author: Lauren B. Alloy, Department of Psychology, Temple University, Weiss Hall, 1701 N. 13th St., Philadelphia, PA 19122. lalloy@temple.edu.

Keywords

Kindling; Stress Sensitization; Bipolar Disorder; Life Events; Course

Kindling of Life Stress in Bipolar Disorder: Comparison of Sensitization and Autonomy Models Bipolar disorder (BD) is a chronic condition that affects an estimated 2–4% of the U.S. population and is one of the leading causes of functional disability among physical and psychological disorders worldwide (Miklowitz & Johnson, 2009). These statistics highlight the need for a better understanding of factors that may influence both the onset and course of the disorder. Studies examining the impact of life events on symptom expression, timing, and severity of affective episodes in BD have made impressive progress toward that goal. Negative life events have been associated with increased likelihood of episodes of bipolar depression, and certain types of negative as well as positive events have been linked to (hypo)manic episode onset (Alloy et al., 2005; Johnson, 2005). Although these studies make important steps toward understanding the role life events play in the development and course of BD, most of this literature assumes a static relationship between psychosocial context and episode onset across the span of the disorder. This is perhaps an incorrect assumption given that numerous studies have pointed toward a significant relationship between number of prior episodes and risk of recurrence (Kendler, Thornton, & Gardner, 2000; Post, Leverich, Xing, & Weiss, 2001).

Overview of the Kindling Hypothesis

The kindling hypothesis (Post, 1992) posits that initial episodes of a mood disorder are more likely to be influenced by psychosocial stressors compared to later episodes, upon which stressors are thought to have less of an effect. The theory is rooted in preclinical studies in which the electrophysiological input needed to elicit seizure activity in rodents progressively declined (“kindling”), whereas rodents developed a behavioral sensitization to stimulant administration (“sensitization”). Based on these findings, Post (1992) hypothesized that life stressors may play an acute pathophysiological role in affective disorders and also serve as stimuli that lower the threshold of stress exposure necessary to trigger a recurrent episode. The kindling hypothesis thus states that initial episodes are likely triggered by major life events (stressors), but that successive episodes grow increasingly more autonomous.

Research suggests, however, that the progressive dissociation between psychosocial stressors and affective episodes may not be the result of a singular process, but may occur via two distinct pathways termed the stress sensitization and stress autonomy models (Monroe and Harkness, 2005). Both models theorize that severe psychosocial stress is not necessary to bring about an affective episode in later stages of the disorder, but suggest different mechanisms for this independence. The sensitization model posits that individuals become increasingly sensitized to environmental stimuli over the course of repeated episodes, such that stressors that may not have been severe enough to initiate first onset are now able to trigger recurrent episodes. Thus, over time, individuals who have experienced more mood episodes would experience a greater frequency of minor events but reduced frequency of major events prior to new episodes, indicating that minor events are increasingly likely to trigger new mood episodes. Major and minor events are thus both

likely to increase risk for new episodes. Alternatively, the stress autonomy model suggests that individuals with BD become progressively less dependent on input from their environment, and an alternative mechanism (possibly an as yet unspecified endogenous neurobiological process; the model has been criticized for its lack of a parsimonious theory as to the mechanism of progressive autonomy) becomes the driving force for future episode recurrence. In other words, major life stress decreases in association with episode recurrence not because smaller "doses" of stress are required to trigger an episode, but rather because episodes become less and less dependent on environmental stress in general. Thus, the autonomy model proposes that over time, individuals who have experienced more mood episodes would experience a lower frequency of both major and minor events prior to new episodes, as well as a weaker relationship between major and minor events and time to episode recurrence, indicating that new episodes are less likely to result from life events.

General Methodological Issues in Life Stress Measurement

The conceptualization and measurement of life stress is inherently challenging. Methodological issues abound in the extant literature, as do inconsistencies in both conceptualization and quantification of life stress (see Bender and Alloy, 2011 for a review of these issues). The concept of "stress" can carry multiple definitions, thus complicating the process of understanding the role such stress plays in the course of affective disorders. For example, stress has been conceptualized to encapsulate "life change events" (i.e., those requiring social readjustment), as well as negative events that can be characterized as distressing. The "severity" of stress then refers to the degree of readjustment required or the intensity of distress experienced, respectively. This is an important distinction because life-change events may be positive (e.g., birth of a child, graduation from college) as well as negative (e.g., bankruptcy, loss of a job).

Studies of kindling in BD commonly have quantified stress by comparing the proportion of patients who experienced at least one life event prior to episode onset. Some studies have suffered from a lack of specificity, in that by examining only the probability of experiencing at least one major life event, they examine whether a general kindling mechanism may exist, but not whether the process would be better explained by a sensitization or autonomy model. Other studies achieved more finely tuned analyses of between-subjects variability in stress levels by calculating total stress scores using sums of raw number of events or of standardized weighted event values. However, despite these methodological advances, these studies hinge upon a potentially faulty assumption that stress exerts "pressure" in an additive fashion, and also fail to examine events according to their objective impact. Thus, there is a great need to understand how stress operates at minor levels in order to conclusively distinguish between stress sensitization and autonomy models.

Existing Research on Kindling in Bipolar Disorder

The literature evaluating kindling in BD is relatively small and fails to offer a clear consensus about how the process may operate (see Bender and Alloy, 2011 for review). Of the fifteen studies conducted, only seven reported a kindling effect, two of which detected kindling within a specific subgroup of patients (with six or more episodes [Bidzinska, 1984]

or with decreasing well intervals [Ehnvall & Ågren, 2002]). Of the four methodologically strongest studies, none reported evidence of kindling in BD. The relatively small number of methodologically sound studies is one of the major limitations of the extant literature on kindling in BD. Issues with data collection (e.g., checklist measures of life events, long retrospective recall intervals), as well as study design are abundant. For example, two studies collapsed across unipolar and bipolar diagnoses (Johnson et al., 2000; Perris, 1984), making it difficult to parse out BD-specific processes. Moreover, many samples were comprised of treatment-seeking participants with long and relatively severe disorder histories. Variation in life stress indices is high across studies, and only one (Hlastala et al., 2000) examined the unique role of minor stressors. This study found that the number of lifetime episodes did not predict events prior to episode onset or in a control period; in contrast, prior to episodes, older individuals experienced more minor events and fewer major events than did younger individuals, suggesting that something specific to aging might underlie changes in the relationship between stress and episodes in BD (Hlastala et al., 2000).

However, no existing studies have carefully examined whether effects were episode polarity-specific or event valence-specific. Thus, even when results point toward a kindling process in BD, the studies did not lend themselves to examinations of whether a sensitization or autonomy model best explained the effects. Therefore, despite the fact that evidence of kindling in BD has been under whelming thus far, there have been too many methodological issues with current research to conclude that the model does not apply.

The Present Study

The present study aimed to conduct a more comprehensive and precise examination of the kindling effect in BD, 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. As initially specified by Monroe and Harkness (2005), in order to adequately test sensitization versus autonomy models, the independent indices of stress frequency (the probability of an antecedent stressor, given the occurrence of an episode) and impact (the probability of a subsequent episode, given the occurrence of a stressful event) must be examined. Also, given that BD studies have found some specificity in the prediction from life events to depressive vs. (hypo)manic episodes (Alloy et al., 2005; Johnson, 2005; Johnson et al., 2008), analyses were conducted separately according to episode polarity.

Overall, we predicted results consistent with a stress sensitization model of BD, rather than a stress autonomy model. 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. Previous research suggests important differences in psychosocial predictors of depression and (hypo)mania. However, BD kindling researchers have failed to distinguish between episodes of different polarity. Thus, hypotheses for the present study were 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.

Polarity-specific hypotheses were formulated according to event valence. Specifically, for all hypotheses, the following predictions applied: (1) the kindling relationship between prior depressive episodes, events, and new prospective depressive episodes would hold for negative events, but not for positive events; and (2) the kindling relationship between prior hypomanic episodes, events, and new prospective (hypo)manic episodes would hold for both negative and positive events.

Method

Participants

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

High GBI participants who met *Diagnostic and Statistical Manual for Mental Disorders* (*DSM-IV*; American Psychiatric Association, 1994) or Research Diagnostic Criteria (RDC; Spitzer, Endicott, & Robins, 1978) for bipolar II, cyclothymia, or bipolar disorder not otherwise specified (BD-NOS) were invited to participate in the longitudinal phase as part of the BSD group. The present study only includes participants who met criteria for bipolar II disorder. Individuals were excluded if they had experienced at least one full-blown manic episode prior to study onset, because an aim of the overall LIBS project was to examine predictors of the progression to bipolar I disorder.[1]

The final LIBS project sample included 227 BSD participants. These participants were representative of the large Phase I screening sample on age, sex, and ethnicity. Following baseline assessment, participants completed regular prospective assessments at four-month intervals (the present sample was followed for an average of 51.5 months [*SD* = 29.3]). Diagnostic interviews were administered at each assessment to collect detailed information on timing, severity, and duration of mood episodes occurring since the previous interview. An independent interviewer, blind to the participant's lifetime and concurrent mood diagnoses, administered a combined Life Events Scale and Life Events Interview (LES and LEI; Francis-Raniere, Alloy, & Abramson, 2006) to collect detailed information about timing, severity, and context of psychosocial events occurring since the last follow-up.

[1]Given that no 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 of the present bipolar II sample are in Table 1. The present study was based on data from all bipolar II participants (n = 44 with bipolar NOS or cyclothymia were excluded)who had complete data for study variables of interest (lifetime history of mood episodes, prospectively assessed mood episodes, and life events; N = 102). Bipolar II participants included and excluded based on these criteria did not significantly differ in gender ($\chi^2(1) = .88$, $p = .35$), age ($t(162) = 1.13$, $p = .26$), or ethnicity ($\chi^2(5) = 1.74$, $p = .88$). Thus, the present sample is representative of the larger LIBS bipolar II project sample. However, power to detect effects was substantially reduced due to loss of participants with missing data. Data were most often missing for number of lifetime episodes. Given that testing kindling models was not a central goal of the LIBS project, although presence of a history of mood episodes was collected for all participants, the precise number of prior episodes was not always collected systematically.

Measures

Phase I Screening Measure

General Behavior Inventory: The revised General Behavior Inventory (GBI; Depue et al., 1989) is a self-report questionnaire used during Phase I to identify potential BSD participants. It contains 73 items, assessing experiences related to depressive, (hypo)manic, or biphasic symptoms on dimensions of intensity, duration, and frequency. The respondent rates each item on 4-point Likert-type scales, ranging from 1 (*not at all*) to 4 (*very often or almost constantly*). Scoring was consistent with the method recommended by Depue and colleagues (1989). GBI cutoffs were previously validated against diagnoses obtained via diagnostic interviews (see Alloy et al., 2008). The GBI has been extensively validated in undergraduates, psychiatric outpatients, and relatives of bipolar I probands (Depue et al., 1981, 1989; Klein, Depue, & Slater, 1985). It has strong internal consistency of α's=.90 – .96, test-retest reliability of r's=.71 – .74, adequate sensitivity (.78), and excellent specificity (.99) and discriminant validity for BSDs (Depue et al., 1981, 1989; Mallon, Klein, Bornstein, & Slater, 1986).

Phase II Diagnostic Interview

Expanded Schedule for Affective Disorders and Schizophrenia – Lifetime Version (exp-SADS-L): The exp-SADS-L (Endicott & Spitzer, 1978) semistructured diagnostic interview was administered during Phase II and assessed the occurrence, duration, and severity of symptoms over the lifetime. The original SADS-L was expanded for the LIBS project to include *DSM-IV* criteria and to increase reliability and accuracy in diagnosing BSDs (see Alloy et al., 2008, 2012 for details of the expansion and interviewer training and supervision).

The exp-SADS-L interview has demonstrated good inter-rater reliability for BSDs (k's > .96) based on 105 jointly rated interviews in the LIBS Project (Alloy et al., 2008). Bipolar II disorder was defined as the occurrence of at least one *DSM-IV* or RDC major depressive and at least one hypomanic episode (see below for episode definitions). As part of the exp-SADS-L diagnostic interview, data were collected on bipolar participants' age at first onset of depression, hypomania, and/or cyclothymia and the number of episodes of each polarity.

Longitudinal Diagnostic Data

Diagnostic Interview: The Expanded SADS – Change (exp-SADS-C; Endicott & Spitzer, 1978) was used to prospectively assess occurrence, timing, duration, and severity of affective episodes throughout each four-month interval. It was expanded in the same way as the SADS-L and allowed diagnosis of both *DSM-IV* and RDC mood episodes (see exp-SADS-L section above; see also Alloy et al., 2008, 2012). Interviewers were blind to participants' GBI status and exp-SADS-L diagnosis. The exp-SADS-C also incorporated 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. Based on 60 jointly rated LIBS Project exp-SADS-C interviews, average kappas were ≥ .80 for mood disorder diagnoses, and ranged from .62 to .98 for severity ratings of individual symptoms (Francis-Raniere et al., 2006). Results of a validity study indicated that participants dated 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

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)that met *DSM-IV* or RDC criteria for a depressive, hypomanic, or manic episode. For testing the frequency component of the kindling model, the index episode was defined as the first prospectively assessed mood episode also preceded by 30 days of euthymia; the sum of events in the 30 days prior to index episode represented the criterion variable. 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. This episode-free control period was necessary to ensure that events occurred prior to the onset of new prospective episodes, rather than potentially resulting from mood episodes, which would confound tests of kindling. For testing the impact component of the kindling model, the index episode was defined as the first prospectively assessed episode of each polarity.

Self-Reported Mood Symptoms—The Beck Depression Inventory (BDI; Beck et al., 1979) is a widely validated 21-item self-report scale of affective, motivational, cognitive, and somatic symptoms of depression. It has good internal consistency, retest reliability, and concurrent validity with clinical depression ratings in both clinical (r = .72) and nonclinical (r = .60) samples, including in undergraduates (Beck, Steer, & Garbin, 1988). The Halberstadt Mania Inventory (HMI; Alloy et al., 1999) is a 28-item self-report questionnaire modeled after the BDI. Like 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 internal consistency (α = .78), construct validity, convergent validity, and discriminant validity, and were significantly correlated (r = .46) with hypomanic symptoms reported during the exp-SADS-C interview (Alloy et al., 1999, 2008). Participants completed the BDI and HMI at the Phase II baseline assessment.

Longitudinal Life Events Data

Life Events Scale: The present study utilized contextual threat methods based on Brown and Harris (1978) with 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 exp-LES was expanded from an earlier 134-item LES (Alloy & Clements, 1992; Needles & Abramson, 1990) and contained 193 items that comprehensively assess positive and negative episodic events across multiple life domains. Items were designed to minimize ambiguity and redundancy, and were eliminated if they reflected symptoms of affective disturbance. Participants indicated whether and how many times each event occurred since the last prospective assessment (approximately 4 month intervals).

A team of raters determined a consensus-based objective severity rating (OSR) and valence (negative/positive) 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*), reflecting the degree to which each event would affect an average individual in average circumstances. Both the original and expanded 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).

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 GBI scores, lifetime diagnosis, 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 used a Life Events Manual containing 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 events not meeting criteria were disqualified by the interviewer. The LEI also facilitated precise dating of event onsets and offsets, using individualized calendars with multiple anchors (e.g., Christmas, 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. Events with COSRs ≥ 3 were categorized as major, whereas those with COSRs ≤ 2 were categorized as minor.

This combined LES/LEI procedure is relatively robust to some of the threats to validity plaguing other life stress studies (see Johnson, 2005). The assessment is thorough and systematic, uses recall aids, and covers a period of only approximately four months. The procedure minimizes reporting bias based on mood state by adhering to stringent, objective event definition criteria and by employing interviewers blind to participants' mood status. This two-phase procedure yields reliable life event information that corresponds well with daily life event reports (Francis-Raniere et al., 2006; Safford et al., 2007).

Statistical Analysis—After conducting preliminary analyses of associations between study variables, we tested the kindling models in two primary ways. First, we evaluated the frequency component, in other words, whether the number of lifetime episodes significantly

predicted the frequency of major events (which were dichotomized as a result of positive skew)and minor events in the 30 days[2] prior to the index episode of depression and hypomania, using linear and logistic regressions, respectively. To account for individual differences in general event levels, in the first step of the models, we included as a covariate the number of life events of the corresponding event type during the 30-day control period. Thus, we were able to conduct an idiographically sensitive analysis of the frequency of life events prior to episode onset, relative to individuals' own general levels of life events. Controlling for control period event levels ensured that results of our hypothesis tests were not confounded by systematic between-subjects differences in life event rates (regardless of the proximity of the observation interval to episode onset).

Second, to evaluate whether the impact of life events on the time until the prospective onset of mood episodes differed based on the number of prior mood episodes, we conducted a series of survival analyses using Cox proportional hazards regressions (Lenze, Cyranowski, Thompson, Anderson, & Frank, 2008; Tabachnik & Fidell, 2007). To adequately disentangle putative sensitization and autonomy processes, models were specified separately for positive and negative event types. We examined whether the interactions between negative events and previous episodes predicted time to new prospective episodes, and then examined whether the interactions between positive events and previous episodes predicted time to new prospective episodes.

The first step of each model contained symptoms of depression and hypomania across the follow-up period prior to the onset of the relevant type of mood episode (for individuals who experienced a mood episode) or end of the study (for individuals who did not experience a mood episode of that type). The second step contained the main effects of 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 variable. Minor life event variables were operationalized as life events per day up until the first prospective episode of each polarity, or end of study if no prospective episode occurred. As a result of positive skew due in part to low frequencies of major events, major event variables were dichotomized according to whether or not individuals experienced a major event across the study prior to the prospective episode onset, or end of study if no prospective episode occurred. The final step contained the main predictor of interest, which was the interaction between events and number of previous affective episodes. We did not control for the number of life events during the control period in the context of survival analyses, because these would be too closely related to the predictor of interest representing life events prior to episode onset. The proportionality of hazards assumption was met in all cases except for major negative events predicting the occurrence of hypomanic episodes, in which case we controlled for the interaction term

[2]Although examining events occurring during a longer euthymic period prior to the index episode of depression or (hypo)mania would increase the frequencies of events potentially relevant to the episode, doing so would have reduced the sample size to the extent that there would be inadequate power to test the hypotheses (e.g., only 43 individuals experienced a three-month period of euthymia immediately prior to the onset of an episode).

between major negative events and the time-dependent covariate (Tabachnick & Fidell, 2007).

Results

Associations Between Study Variables

Gender and age were not associated with any study variables. Zero-order correlations among study variables, mean numbers of event types, and percentage of participants with at least one event of each type are presented in the supplemental tables.

Tests of Kindling: Frequency of Life Events—In these analyses, we examined the frequency component of the kindling models. Polarity-specific hierarchical linear regression analyses were conducted to examine whether the number of lifetime episodes significantly predicted major and minor event levels in the 30 days prior to index episode (pre-episode period), controlling for events in the within-subjects control period. Based on the sensitization model, we hypothesized that more previous episodes would prospectively predict fewer major events but more minor events during the 30-day pre-episode periods.

Table 2 presents results of multiple linear or logistic (in the case of major events) regression analyses examining the relationship between lifetime history of depression and 30-day sums (or presence/absence)of life events prior to prospective depressive episodes. More lifetime depressive episodes predicted a significantly higher frequency of minor negative events prior to prospective depressive episodes. The number of lifetime depressive episodes did not prospectively predict major negative and major and minor positive event frequencies prior to prospective episodes of depression.[3]

Table 2 also presents results of multiple linear or logistic regression analyses examining the relationship between lifetime history of (hypo)mania and 30-day sums (or presence/absence) of life events prior to prospective hypo)mania. More lifetime hypomanic episodes predicted a significantly higher frequency of minor positive events prior to prospectively assessed (hypo)manic episodes. In all other cases, number of lifetime hypomanic episodes did not predict event frequencies prior to prospective (hypo)manic episodes.[4]

Impact of Life Events

Relationship between lifetime episodes and time to prospective onset of mood episodes: Results of Cox regression analyses examining the relationship between lifetime episodes and time from the beginning of the study to the prospective onset of new episodes are presented in Tables 3 and 4. The average lengths of the follow-up intervals prior to the onset of depression and hypomania (or end of study if no episode was experienced) were 14.3 months (*SD* = 14.2) and 18.3 months (*SD* = 7.2), respectively. Eighty percent of the sample experienced a prospective onset of depression across follow-up, whereas 20% were censored in Cox regression analyses because they did not have an onset of depression. Sixty-four percent of the sample experienced a prospective onset of hypomania across follow-up, with

[3]Results were comparable when using continuous (non-dichotomous) major event variables.
[4]Results were comparable when using continuous (non-dichotomous) major event variables.

the remaining 36% censored. We predicted that participants with a greater number of lifetime episodes would experience a shorter time to new prospective episode. Consistent with hypotheses, lifetime depressive episodes predicted a shorter time to the prospective onset of depressive episodes, and lifetime (hypo)manic episodes predicted shorter time to the prospective onset of (hypo) manic episodes (Table 3), although the significance of these terms differed depending on which life event covariates were included in the analyses.

Relationship between life events and time to prospective onset of mood episodes: We also hypothesized that the presence of major events (Table 3) and greater numbers of minor events (Table 4) would predict shorter time to onset of new prospective episodes. More minor negative events predicted a shorter time to onset of depression. However, major negative and major positive events predicted a *longer* time until onset of depression,[5] and minor positive events did not predict time to depression.

Among models predicting (hypo)mania, both more negative and more positive minor events predicted a significantly shorter time to onset of (hypo)mania. However, more negative and positive major events predicted a significantly *longer* time to onset of (hypo)mania.[6]

Test of the kindling models: Moderating effects of lifetime episodes on impact of life events: In line with a stress sensitization model, we hypothesized 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. Thus, the main predictor of interest was the interaction between number of previous lifetime episodes and the number of life events prior to prospective onset of episodes.

Inconsistent with hypotheses, lifetime depressive episodes did not interact with any life event category to predict time to onset of prospective depressive episodes, and lifetime hypomanic episodes also did not interact with any life event category to predict time to onset of prospective hypomanic episodes, providing little support for either sensitization or autonomy models of kindling.

Discussion

This study aimed to conduct a comprehensive and precise examination of the kindling effect as it applies to bipolar II disorder, thereby allowing for a direct comparison of sensitization and autonomy models. We predicted that results would support a stress sensitization rather than a stress autonomy model. That is, we predicted that as the number of previous episodes increased, there would be a decreased frequency of major events, an increased frequency of minor events, and an increased impact of both major and minor events. Effects were predicted to be polarity-specific: depressive episodes would be associated with negative

[5]When using major events per day rather than dichotomizing major events, neither major negative events nor major positive events significantly predicted time until onset of depressive episodes.

[6]When using major events per day rather than dichotomizing major events, major positive events did not predict time until onset of hypomanic episodes; major negative events continued to predict longer time until onset of hypomanic episodes.

events, whereas (hypo)manic episodes would be associated with negative and positive events.

Globally, our results were partially in line with a sensitization model, but additional findings would be needed to fully support this model. Prior to prospective depression, more lifetime episodes predicted an increased frequency of minor, but not major, negative events. Prior to prospective (hypo)mania, more lifetime episodes predicted an increased frequency of minor, but not major, positive events. These results were consistent with our hypotheses in that individuals with bipolar II who have experienced more lifetime mood episodes may experience more frequent minor events prior to new mood episodes, and that the types of minor events that occur prior to new episodes may be polarity-specific. However, inconsistent with sensitization hypotheses, we did not find evidence that individuals with more lifetime episodes experienced lower frequencies of major negative events prior to depression and lower frequencies of major positive events prior to hypomania. Additionally, the number of past mood episodes did not moderate the relationship between life events and the onset of new episodes of depression or hypomania, failing to provide support for either sensitization or autonomy models of kindling.

In terms of main effects of the impact of events on time to recurrence, all dichotomized major event types predicted a longer time to recurrence of both episode polarities. One possible reason that major negative events predicted a longer time until the onset of (hypo)mania is that major events such as losses or failures may deactivate the behavioral approach system (BAS), reducing the likelihood of activated states such as (hypo)mania (e.g., Johnson, 2005; Urosevic et al., 2008). It was surprising that major positive events predicted a *longer* time until the onset of (hypo)mania, given that a subset of major positive events may be events such as goal-attainment events that are likely to activate the BAS, leading to (hypo)mania (Urosevic et al., 2008). Major positive events also predicted a longer time until the onset of depression, consistent with the notion that positive events may reduce the likelihood of depression (e.g., Needles & Abramson, 1990). Inconsistent with hypotheses, major negative events predicted a *longer* time until the onset of depression. This finding was surprising given that major negative events are thought to precipitate episodes of depression in bipolar disorder (Johnson, 2005). One possible explanation for these counterintuitive findings is that they may be a result of a systematic bias in the periods in which life events were evaluated in the present study. Because our measure only used life events that occurred prior to the onset of the first prospective mood episode, individuals who did not experience a mood episode had a longer period of time (until the end of the study) in which to experience life events, increasing the probability that they experienced a major event within the time frame. Thus, the findings that major negative events predicted a longer time until the onset of depression, and that major negative and positive events predicted a longer time until the onset of (hypo)mania, may be due to differential periods of follow-up for gathering life events. Indeed, when conceptualizing major events as events per day of follow-up (rather than dichotomizing them based on occurrence or non-occurrence), neither of these counterintuitive results remained.

In contrast, in line with hypotheses, minor positive and minor negative events predicted a shorter time to the onset of (hypo)mania. It is possible that different types of minor negative

events could have differential impact on symptoms of (hypo)mania. For example, two of the most common minor negative events that occurred prior to onset of (hypo)mania were sleep being frequently disrupted due to negative conditions (an event that by definition leads to sleep loss and social rhythm disruption, which is likely to precipitate mood symptoms in individuals with bipolar disorder; Alloy, Nusslock, & Boland, in press) and having a fight with a significant other (which potentially could result in anger, activating the BAS, and thus, hypomanic symptoms; Carver, 2004). Additionally, as hypothesized, minor negative events predicted a shorter time until the onset of depression; in contrast, minor positive events did not predict time until depression.

In summary, more previous episodes predicted an increased frequency of polarity-specific minor events, and an increased likelihood of experiencing the onset of depression or (hypo)mania, but did not appear to influence the impact of life events on the onset of mood episodes. This pattern of findings is partially consistent with a stress sensitization model. However, within specific event types and polarities, no complete patterns of stress sensitization emerged. The current study provided no support for a stress autonomy model, because contrary to the predictions of the autonomy model, there was an increased frequency of minor events, and there was not a decreased impact of events on prospective episodes.

It is possible that the valence-based event-coding scheme did not fully capture stress sensitization processes that may be occurring. This may indicate that this theoretical approach to conceptualizing life events is inadequate, or that measurement error (e.g., forgetting, recall bias, imprecision due to use of *a priori* event codes) confounded results. However, our 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 elevated frequency of minor negative events, whereas (hypo)mania was associated only with elevated frequency of minor positive events. It is possible that evaluating theoretically-driven components of life events, such as the extent to which events activate or deactivate the BAS and/or lead to social rhythm disruption (Alloy et al., in press) could help to more precisely capture sensitization or autonomy processes.

One possible reason that our results did not show decreased frequency of major events prior to mood episodes may be that a longer observation interval is needed, given that major events occur relatively infrequently (ranging from 27–41% of our sample in the 30-day periods prior to episodes). Another reason for the lack of support for kindling hypotheses in the prospective impact analyses may be that it would be preferential to evaluate events occurring in the interval between the offset of the last episode and the onset of the next episode, rather than only measuring events from the study baseline until next episode. Using the study baseline (e.g., the previous episode for one participant may have offset the day prior to study baseline, whereas the previous episode for another participant may have offset years prior to study baseline) is a limitation that exclusively affects impact analyses, and not frequency analyses. Alternatively, this window of observation (which could be up to four years) might be too long, as events occurring at the beginning of this window might be unlikely to precipitate the occurrence of mood episodes several years later. It is possible that considering a different threshold of severity for major and minor events also would lead to

different patterns of results. Additionally, we did not distinguish between episodic and chronic life stressors, which potentially could have different impacts on the onset of episodes, or could moderate the impact of each other on episodes. Future longitudinal research also might evaluate within-subjects tests of sensitization vs. autonomy (evaluating how individuals' own propensities to experience mood episodes following life events changes over time with increasing numbers of episodes) rather than using between-subjects tests as we did in this study. Nevertheless, the present study is the first to have examined kindling in BD while making careful, theory-driven distinctions regarding episode polarities 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 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 accounted for a 6% increase in variance; the addition of lifetime hypomanic episodes in the model predicting to minor positive events resulted in a 9% increase in variance explained. Among significant models, the overall model accounted for 7% – 11% of the variance in event levels. This is not surprising, given that statistical models in the present study predicted to outcomes that are likely multiply-determined and highly complex.

Clinical Implications

Although results from the present study warrant further replication, there are important therapeutic implications related to empirical findings on kindling processes in bipolar II disorder. Results of this study suggest that it may be important to incorporate illness progression into treatment conceptualization. As the course of the disorder progresses, individuals with bipolar II 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 disorder history. Affective consequences conferred by a given stressor may be determined by the relative relationship between the intensity of the environmental stressor and the robustness of the individual's ability to adapt (Monroe, 2008). According to the stress sensitization hypothesis, but only partially in line with the present findings, successive mood episodes in bipolar disorder might serve to weaken adaptive processes. If adaptive processes weaken over time, a lower intensity of stress would be required to produce the same affective response. The individual's ability to adapt to psychosocial changes could evolve across the course of the disorder and be affected by a number of underlying factors that have been implicated in psychopathology in general (e.g., changes in the hypothalamic-pituitary-adrenal axis regulation of cortisol; see Monroe, 2008) and BD in particular (e.g., social rhythm irregularity; see Grandin, Alloy, & Abramson, 2006). Thus, the sensitization model would suggest that a job loss may confer a higher vulnerability to relapse for an individual with a history of more bipolar episodes, relative to one 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 (2007) 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 improve adaptability 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.

Strengths and Limitations

The present study built upon existing research and had several notable strengths. First, this prospective longitudinal investigation followed bipolar II 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. Thus, life events were assessed via rigorous standardized interviews with demonstrated high reliability and validity. Interviewer bias was minimized by keeping life events interviewers blind 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 BSDs. Frequency- and impact-related findings emerged for both major and minor event categories, thus underscoring the importance of examining less severe events.

The present study also was the first prospective study to use a polarity-specific and event valence-specific approach to testing the kindling hypothesis. Individuals with milder forms of BD such as bipolar II disorder are less likely to be treatment-seeking than those with bipolar I, so our study may allow for a more naturalistic approach to the examination of kindling effects. In light of its prospective design, rigorous data collection techniques, polarity-specific analyses of frequency and impact at both major and minor levels of event severity (which, in turn, allows for a comparison of sensitization and autonomy models of kindling), and use of valence-based 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 provided relatively low power to detect hypothesized effects. Participants included in the final sample were demographically representative of the larger LIBS project sample, but some statistical power was lost because of missing data. Participants were necessarily excluded from analyses in which they did not have a qualifying observation period, thereby further reducing power to detect effects. However, the final sample size for the present study was larger than all previous prospective investigations of kindling in BD (see Bender and 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, but these studies may have included events that were confounded with the occurrence of mood episodes. We were unable to test hypotheses

using three-month periods because this would have further substantially reduced the number of participants with qualifying episode-free intervals. This, in turn, would lead to a further reduction in statistical power. Given that mood episodes in bipolar disorder are generally briefer and more frequent than are those in unipolar depression (Cusin et al., 2000; Goodwin & Jamison, 2007), it is not surprising that a proportion of our bipolar II participants did not have three-month long episode-free intervals. To provide a rigorous test of the sensitization and autonomy models, it is necessary to only use life events that occurred in an interval prior to prospective mood episodes during which the participant was euthymic; otherwise, the occurrence of additional mood episodes during the event interval confounds the analyses, and the events may be the result of mood episodes rather than a potential trigger of new prospective episodes. However, if our sample size allowed, kindling processes may have been more easily detected during the three months prior to episode onset, rather than one month.

We also were not able to evaluate the degree to which stress was actively generated by our participants, given the lack of contextually-based ratings of dependence or independence of life events. It is possible that a greater number of lifetime mood episodes would contribute to the occurrence of more dependent events, which then might increasingly confound an examination of kindling processes as the disorder progresses. Moreover, the generation of stressful events may be more likely to occur at the minor rather than the major event severity range. However, our inclusion in the analyses of only participants who had at least a one-month euthymic interval prior to their prospective onset of mood episodes was designed to mitigate the possibility that the events were dependent on participants' current mood or a recent mood episode. Also, we did not have systematic prospective data about participation in psychotherapy so could not examine whether engagement in treatment would moderate the effects of life events on mood episodes.

Results warrant replication before generating firm theoretical or clinical conclusions. In addition, sample generalizability should be considered carefully. For frequency analyses, it was necessary to exclude participants who did not experience at least one prospective episode 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 was no 30-day period of euthymia. Thus, the final sample was biased towards participants who experienced episodes, but also who had longer inter-episode periods of euthymia. Results may not generalize to individuals with rapid-cycling forms of BD. 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 BD has focused primarily on individuals with bipolar I. Although use of a bipolar II sample represents a novel contribution to the literature, it also is possible that sensitization or autonomy is more clearly apparent at higher ends of the spectrum of episode severity. Individuals who have experienced more severe mood episodes (e.g., as in the case of mania in bipolar I disorder) that were initially triggered by major events potentially would be more likely to become sensitized to stress, such that these pathways are more easily activated by future events; alternatively, subsequent episodes

could appear to occur more autonomously as a result of increasing sensitivity to reward or other unspecified endogenous neurobiological mechanisms. Participants in this study 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 mean age of the sample may have affected results. Given that the sample was relatively young, it may have been more difficult to find evidence for kindling in our sample because participants may have experienced fewer mood episodes than older individuals. On the other hand, the sample was mostly comprised of participants who already had experienced several lifetime episodes. This may have impacted results, because some evidence suggests that kindling effects are most evident earlier in the course of the disorder (Ehnvall & Ågren, 2002; 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). Relatedly, the young adult sample in our study may have resulted in a systematic bias toward the overall occurrence of minor events relative to older and/or primarily working adults with bipolar disorder who might be more likely to experience events with more major impact (e.g., marriage, family death, job loss, change in financial status or job, divorce, children with difficulties, etc.). Future work could evaluate changes in exposure to different types of life events relative to individuals' age.

Similarly, if kindling processes are most evident early in the course of the illness, they may be more difficult to detect using prospective study designs among older bipolar adults. Our sample might be considered to have a relatively early onset of BD. Much research has examined differences between individuals with early- vs. late-onset BD. For example, early-onset individuals may have a higher genetic loading for BD, which may ameliorate the degree of influence attributable to environmental events. Moreover, although age did not significantly impact life event rates within the present study, our participant age range was small and other studies on kindling in BD have focused on older samples. In one methodologically strong study, Hlastala and colleagues (2000) found evidence that something specific to the aging process may underlie developmental changes in the stress-episode relationship. Nevertheless, we believe that our study performed very conservative tests of the sensitization and autonomy hypotheses, not only because our bipolar II participants were young adults, but also because we required a one-month euthymic period before prospective mood episodes and controlled for the number of life events experienced during control periods without episodes.

Directions for Future Research

Despite some limitations, this study represents an important methodological and theoretical advancement on kindling in BD. Future studies may build upon the present one in several ways. First, a larger sample size would increase power to detect kindling-related effects. Longer follow-up periods also would increase the likelihood that participants experience qualifying observation periods. Individuals ideally would be followed starting prior to their initial onset of BD, over an extensive time span to better delineate 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. This statistical and methodological approach would also enable analyses of event impact using a “true” baseline. Such an approach would greatly advance knowledge of this complex developmental process. Genetic or behavioral high-risk samples are ideal for examining phenomena that occur at such low base rates.

Future research also should examine subgroups of BSD individuals with differing course trajectories and severities of illness. Many individuals with bipolar disorder experience faster episode recurrence over time, whereas others may show episode stability or deceleration (Ehnvall & Ågren, 2002; Goldberg & Harrow, 1994; Post, 1992). The ability to compare stress sensitivity between individuals with bipolar I, bipolar II, and cyclothymia may be illuminating as well. It is important to enhance our understanding of the role of life stress across the range of bipolar illness expression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Alloy LB, Abramson LY. The Temple-Wisconsin Cognitive Vulnerability to Depression (CVD) Project: Conceptual background, design, and methods. Journal of Cognitive Psychotherapy: An International Quarterly. 1999; 13:227–262.

Alloy LB, Abramson LY, Urošević S, Walshaw PD, Nusslock R, Neeren AM. The psychosocial context of bipolar disorder: Environmental, cognitive, and developmental risk factors. Clinical Psychology Review. 2005; 25(8):1043–1075. [PubMed: 16140445]

Alloy LB, Abramson LY, Walshaw PD, Cogswell A, Hughes ME, Iacoviello BM, et al. Behavioral Approach System (BAS) and Behavioral Inhibition System (BIS) sensitivities and bipolar spectrum disorders: Prospective prediction of bipolar mood episodes. Bipolar Disorders. 2008; 10:310–322. [PubMed: 18271911]

Alloy LB, Bender RE, Whitehouse WG, Wagner CA, Liu RT, et al. High behavioral approach system (BAS) sensitivity, reward responsiveness, and goal-striving predict first onset of bipolar spectrum disorders: A prospective behavioral high-risk design. Journal of Abnormal Psychology. 2012; 121:339–351. [PubMed: 22004113]

Alloy LB, Clements CM. Illusion of control: invulnerability to negative affect and depressive symptoms after laboratory and natural stressors. Journal of Abnormal Psychology. 1992; 101(2): 234–245. [PubMed: 1583214]

Alloy LB, Nusslock R, Boland EM. The development and course of bipolar spectrum disorders: An integrated reward and circadian rhythm dysregulation model. Annual Review of Clinical Psychology. in press.

Alloy LB, Reilly-Harrington N, Fresco DM, Whitehouse WG, Zechmeister JS. Cognitive styles and life events in subsyndromal unipolar and bipolar disorders: Stability and prospective prediction of depressive and hypomanic mood swings. Journal of Cognitive Psychotherapy. 1999; 13(1):21–40.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders (. 4. Washington DC: 1994.

Beck, AT.; Rush, AJ.; Shaw, BF.; Emery, G. Cognitive therapy of depression. New York: Guilford Press; 1979.

Beck AT, Steer RA, Garbin MG. Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. Clinical Psychology Review. 1988; 8:77–100.

Bender RE, Alloy LB. Life stress and kindling in bipolar disorder: Review of the evidence and integration with emerging biopsychosocial theories. Clinical Psychology Review. 2011; 31:383–398. [PubMed: 21334286]

Bidzinska EJ. Stress factors in affective diseases. British Journal of Psychiatry. 1984; 144:161–166. [PubMed: 6704602]

Brown, GW.; Harris, T. Social origins of depression: A study of psychiatric disorder in women. New York: Free Press; 1978.

Carver CS. Negative affect deriving from the behavioral approach system. Emotion. 2004; 4:3–22. [PubMed: 15053723]

Depue RA, Krauss S, Spoont MR, Arbisi P. General Behavior Inventory identification of unipolar and bipolar affective conditions in a nonclinical university population. Journal of Abnormal Psychology. 1989:117–126. [PubMed: 2708652]

Depue RA, Slater J, Wolfstetter-Kausch H, Klein D, Goplerud E, Farr D. A behavioral paradigm for identifying persons at risk for bipolar depressive disorder: A conceptual framework and five validation studies. Journal of Abnormal Psychology. 1981; 90:381–437. [PubMed: 7298991]

Ehnvall A, Ågren H. Patterns of sensitisation in the course of affective illness: A life-charting study of treatment-refractory depressed patients. Journal of Affective Disorders. 2002; 70(1):67–75. [PubMed: 12113921]

Endicott J, Spitzer RL. A diagnostic interview: The schedule for affective disorders and schizophrenia. Archives of General Psychiatry. 1978; 35(7):837–844. [PubMed: 678037]

Francis-Raniere EL, Alloy LB, Abramson LY. Depressive personality styles and bipolar spectrum disorders: Prospective tests of the event congruency hypothesis. Bipolar Disorders. 2006; 8(4): 382–399. [PubMed: 16879139]

Grandin LG, Alloy LB, Abramson LY. The social zeitgeber theory, circadian rhythms, and mood disorders: Review and evaluation. Clinical Psychology Review. 2006; 26:679–694. [PubMed: 16904251]

Goldberg JF, Harrow M. Kindling in bipolar disorders: A longitudinal follow-up study. Biological Psychiatry. 1994; 35(1):70–72. [PubMed: 7909451]

Hlastala SA, Frank E, Kowalski J, Sherrill JT, Tu XM, Anderson B, et al. Stressful life events, bipolar disorder, and the 'kindling model'. Journal of Abnormal Psychology. 2000; 109(4):777–786. [PubMed: 11196004]

Johnson L, Andersson-Lundman G, Aberg-Wistedt A, Mathe AA. Age of onset in affective disorder: Its correlation with hereditary and psychosocial factors. Journal of Affective Disorders. 2000; 59(2):139–148. [PubMed: 10837882]

Johnson SL. Life events in bipolar disorder: towards more specific models. Clinical Psychology Review. 2005; 25(8):1008–1027. [PubMed: 16129530]

Johnson SL, Cueller AK, Ruggero C, Winett-Perlman C, Goodnick P, White R, et al. Life events as predictors of mania and depression in bipolar I disorder. Journal of Abnormal Psychology. 2008; 117(2):268–277. [PubMed: 18489203]

Kendler KS, Thornton LM, Gardner CO. Stressful life events and previous episodes in the etiology of major depression in women: An evaluation of the 'Kindling' hypothesis. American Journal of Psychiatry. 2000; 157(8):1243–1251. [PubMed: 10910786]

Klein DN, Depue RA, Slater JF. Cyclothymia in the adolescent offspring of parents with bipolar affective disorder. Journal of Abnormal Psychology. 1985; 94:115–127. [PubMed: 3998280]

Lenze SN, Cyranowski JM, Thompson WK, Anderson B, Frank E. The cumulative impact of nonsevere life events predicts depression recurrence during maintenance treatment with interpersonal psychotherapy. Journal of Consulting and Clinical Psychology. 2008; 76(6):979–987. [PubMed: 19045966]

Mallon JC, Klein DN, Bornstein RF, Slater JF. Discriminant validity of the General Behavior Inventory: An outpatient study. Journal of Personality Assessment. 1986; 50:568–577. [PubMed: 3820050]

Mazure C. Life stressors as risk factors in depression. Clinical Psychology: Science and Practice. 1998; 5:291–313.

Miklowitz DJ, Johnson SL. Social and familial factors in the course of bipolar disorder: Basic processes and relevant interventions. Clinical Psychology: Science and Practice. 2009; 16(2):281–296. [PubMed: 19684882]

Monroe SM. Modern approaches to conceptualizing and measuring human life stress. Annual Review of Clinical Psychology. 2008; 4:33–52.

Monroe SM, Harkness KL. Life stress, the “kindling” hypothesis, and the recurrence of depression: Considerations from a life stress perspective. Psychological Review. 2005; 112(2):417–445. [PubMed: 15783292]

Monroe SM, Roberts JR. Conceptualizing and measuring life stress: Problems, principles, procedures, and progress. Stress Medicine. 1990; 6:209–216.

Needles DJ, Abramson LY. Positive life events, attributional style, and hopelessness: Testing a model of recovery from depression. Journal of Abnormal Psychology. 1990; 99:156–165. [PubMed: 2348009]

Perris H. Life events and depression: II. Results in diagnostic subgroups, and in relation to the recurrence of depression. Journal of Affective Disorders. 1984; 7(1):25–36. [PubMed: 6236241]

Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. American Journal of Psychiatry. 1992; 149:999–1010. [PubMed: 1353322]

Post RM. Kindling and sensitization as models for affective episode recurrence, cyclicity, and tolerance phenomena. Neuroscience and Biobehavioral Reviews. 2007; 31(6):858–873. [PubMed: 17555817]

Post RM, Leverich GS, Xing G, Weiss RB. Developmental vulnerabilities to the onset & course of bipolar disorder. Developmental Psychopathology. 2001; 13:581–598.

Safford SM, Alloy LB, Abramson LY, Crossfield AG. Negative cognitive style as a predictor of negative life events in depression-prone individuals: A test of the stress generation hypothesis. Journal of Affective Disorders. 2007; 99(1–3):147–154. [PubMed: 17030064]

Shapiro, RW.; Keller, MB. Longitudinal Interval Follow-up Evaluation (LIFE). Boston, MA: 1979.

Spitzer RL, Endicott J, Robins E. Research diagnostic criteria: Rationale and reliability. Archives of General Psychiatry. 1978; 35(6):773–782. [PubMed: 655775]

Tabachnick, BG.; Fidell, LS. Using multivariate statistics. 5. Boston: Allyn and Bacon; 2007.

Urošević S, Abramson LY, Harmon-Jones E, Alloy LB. Dysregulation of the behavioral approach system (BAS) in bipolar spectrum disorders: Review of theory and evidence. Clinical Psychology Review. 2008; 28(7):1188–1205. [PubMed: 18565633]

Table 1

Demographic and Clinical Characteristics of Study Participants

Demographics	
Gender	
Male	37.3%
Female	62.7%
Age, years (*SD*)	20.71 (1.74)
Ethnicity	
Caucasian	68.6%
African American	13.7%
Asian	2.9%
Hispanic	2.0%
Other	12.7%
Lifetime Episodes, mean (*SD*)	
Lifetime depressive episodes	3.57 (1.56)
Age at onset of depressive episodes	16.01 (3.79)
Lifetime hypomanic episodes	3.03 (1.51)
Age at onset of hypomanic episodes	14.59 (4.76)
Prospective Episodes	
Occurrence of major depressive episode	80.4%
Occurrence of (hypo)manic episode	64.7%

Note. SD = Standard deviation

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Table 2

Linear or Logistic Regression Models with Lifetime History of Episodes Predicting Events in 30 Days Prior to Prospective Depression or (Hypo)mania

	Prospective Depression (*n*= 66)				Prospective (Hypo)mania (*n*= 57)			
Predictor	***B***	**S.E. *B***	**β or Wald χ^2**	**ΔR^2**	***B***	**S.E. *B***	**β or Wald χ^2**	**ΔR^2**
Major Negative								
Step 1								
Control Period Major Neg.	0.22	0.50	0.20	<.01	0.92	0.58	2.53	.06
Step 2								
Control Period Major Neg.	0.21	0.51	0.18	<.01	0.80	0.60	1.76	.01
Lifetime Episodes	−0.03	0.16	0.04		−0.14	0.22	0.39	
Minor Negative								
Step 1								
Control Period Minor Neg.	0.12	0.14	0.11	.01	0.21	0.20	0.14	.02
Step 2								
Control Period Minor Neg.	0.12	0.13	0.11	.06	0.25	0.20	0.17	.03
Lifetime Episodes	1.07	0.52	0.25*		1.11	0.81	0.19	
Major Positive								
Step 1								
Control Period Major Pos.	0.35	0.60	0.35	.01	−0.80	0.84	0.93	.03
Step 2								
Control Period Major Pos.	0.35	0.60	0.35	<.01	−0.86	0.84	1.04	.03
Lifetime Episodes	−0.02	0.18	0.01		0.25	0.23	1.16	
Minor Positive								
Step 1								
Control Period Minor Pos.	0.21	0.12	0.21^	.05	0.09	0.10	0.13	.02
Step 2								
Control Period Minor Pos.	0.21	0.12	0.22^	.03	0.10	0.10	0.13	.09
Lifetime Episodes	0.45	0.30	0.18		0.93	0.40	0.30*	

^ $p < .10$;

* $p < .05$;

** $p<.01$.

Note. Major events were dichotomized representing presence (yes/no) of a major event. Analyses involving major events used logistic regression. The sample in this table is smaller than the overall sample as a result of the requirements (1) to have experienced a mood episode, and (2) to have experienced a one-month euthymic period immediately prior to the episode.

Table 3

Cox Regression Models of Major Events Interacting with History of Episodes to Predict Time to Onset of Prospective Depression and (Hypo)mania Episodes

	Prospective Depression							Prospective (Hypo)mania						
						95% CI							95% CI	
Predictor	**B**	**S.E. B**	**Wald**	***P***	**OR**	**Lower**	**Upper**	**B**	**S.E. B**	**Wald**	***P***	**OR**	**Lower**	**Upper**
Major Negative Events														
Step 1														
BDI	0.03	0.01	4.31	**.04**	1.03	1.00	1.05	0.02	0.02	1.77	.18	1.02	0.99	1.05
HMI	0.01	0.02	0.32	.57	1.01	0.98	1.05	0.05	0.02	6.57	**.01**	1.05	1.01	1.08
Step 2														
BDI	0.02	0.01	1.16	.28	1.02	0.99	1.04	0.02	0.01	1.40	.24	1.02	0.99	1.05
HMI	0.03	0.02	2.14	.14	1.03	0.99	1.06	0.04	0.02	3.67	.06	1.04	1.00	1.07
Episodes	0.03	0.02	3.14	.08	1.03	1.00	1.07	<0.01	<0.01	0.81	.37	1.00	1.00	1.01
Major Negative Events	−1.29	0.26	25.39	**<.01**	0.28	0.17	0.45	−1.55	0.26	36.48	**<.01**	0.21	0.13	0.35
Step 3														
BDI	0.02	0.01	1.26	.26	1.02	0.99	1.04	0.02	0.01	1.42	.23	1.02	0.99	1.05
HMI	0.03	0.02	2.64	.10	1.03	0.99	1.07	0.04	0.02	4.55	**.03**	1.04	1.00	1.08
Episodes	0.07	0.04	2.26	.13	1.07	0.98	1.16	−0.01	0.01	1.46	.23	0.99	0.98	1.00
Major Negative Events	−3.57	1.31	7.43	**<.01**	0.03	<0.01	0.37	−1.84	0.30	38.52	**<.01**	0.16	0.09	0.28
Episodes x Major Neg. Events	−0.04	0.05	0.55	.46	0.97	0.88	1.06	0.01	0.01	2.91	.09	1.01	1.00	1.02
Major Negative Events x Time	0.51	0.25	4.29	**.04**	1.67	1.03	2.70							
Major Positive Events														
Step 1														
BDI	0.03	0.02	4.31	**.04**	1.03	1.00	1.05	0.02	0.02	1.77	.18	1.02	0.99	1.05
HMI	0.01	0.02	0.32	.57	1.01	0.98	1.05	0.05	0.02	6.57	**.01**	1.05	1.01	1.08
Step 2														
BDI	−0.01	0.02	0.86	.35	0.99	0.96	1.02	−0.01	0.02	0.60	.43	0.99	0.96	1.02
HMI	0.04	0.02	4.68	**.03**	1.04	1.00	1.08	0.04	0.02	4.73	**.03**	1.04	1.00	1.08
Episodes	0.05	0.02	7.95	**.01**	1.05	1.02	1.09	<0.01	<0.01	5.63	**.02**	1.00	1.00	1.00
Major Positive Events	−1.96	0.29	44.46	**<.01**	0.14	0.08	0.25	−1.85	0.28	43.78	**<.01**	0.16	0.09	0.27

	Prospective Depression							Prospective (Hypo)mania						
						95% CI							95% CI	
Predictor	**B**	**S.E. B**	**Wald**	***P***	**OR**	**Lower**	**Upper**	**B**	**S.E. B**	**Wald**	***P***	**OR**	**Lower**	**Upper**
Step 3														
BDI	−0.01	0.02	0.67	.41	0.99	0.96	1.02	−0.01	0.02	0.44	.51	0.99	0.96	1.02
HMI	0.04	0.02	4.74	**.03**	1.04	1.00	1.08	0.04	0.02	4.97	**.03**	1.04	1.01	1.08
Episodes	0.11	0.04	7.42	**.01**	1.12	1.03	1.21	>−0.01	0.01	0.04	.84	1.00	0.98	1.01
Major Positive Events	−1.49	0.43	12.23	**<.01**	0.23	0.10	0.52	−1.91	0.30	39.97	**<.01**	0.14	0.08	0.27
Episodes x Major Pos. Events	−0.07	0.05	2.69	.10	0.93	0.85	1.01	<0.01	0.01	0.22	.64	1.00	0.99	1.02

Note. BDI = Mean Beck Depression Inventory score from baseline to first onset of episode or end of study; HMI = Mean Halberstadt Mania Inventory score from baseline to first onset of episode or end of study; Time = time-dependent covariate (included for any predictor for which proportionality of risk assumption was not upheld; Tabachnik & Fidell, 2007).

Table 4

Cox Regression Models of Minor Events Interacting with History of Episodes to Predict Time to Onset of Prospective Depression and (Hypo)mania Episodes

	Prospective Depression							Prospective (Hypo)mania						
						95% CI							95% CI	
Predictor	**B**	**S.E. B**	**Wald**	***P***	**OR**	**Lower**	**Upper**	**B**	**S.E. B**	**Wald**	***P***	**OR**	**Lower**	**Upper**
Minor Negative Events														
Step 1														
BDI	0.03	0.02	4.31	**.04**	1.03	1.00	1.05	0.02	0.02	1.77	.18	1.02	0.99	1.05
HMI	0.01	0.02	0.32	.57	1.01	0.98	1.05	0.05	0.02	6.57	**.01**	1.05	1.01	1.08
Step 2														
BDI	0.03	0.01	4.71	**.03**	1.03	1.00	1.06	0.02	0.02	2.02	.16	1.02	0.99	1.05
HMI	0.01	0.02	0.43	.51	1.01	0.98	1.05	0.05	0.02	2.71	**.01**	1.05	1.01	1.09
Episodes	0.02	0.02	0.82	.37	1.02	0.98	1.06	<0.01	<0.01	0.67	.41	1.00	1.00	1.00
Minor Negative Events	1.46	0.50	8.56	**<.01**	4.30	1.62	11.43	1.87	0.37	24.98	**<.01**	6.46	3.11	13.44
Step 3														
BDI	0.02	0.01	3.61	.06	1.03	1.00	1.06	0.02	0.02	1.76	.28	1.02	0.99	1.05
HMI	0.01	0.02	0.71	.40	1.02	0.98	1.05	0.05	0.02	6.61	**.01**	1.05	1.01	1.09
Episodes	−0.01	0.02	0.08	.78	0.99	0.95	1.04	<0.01	<0.01	1.97	.16	1.00	1.00	1.01
Minor Negative Events	−0.34	1.22	0.08	.78	0.71	0.07	7.73	2.02	0.39	26.63	**<.01**	7.52	3.49	16.18
Episodes x Minor Neg. Events	0.20	0.12	2.92	.09	1.22	0.97	1.54	>−0.01	0.01	1.10	.29	1.00	0.99	1.00
Minor Positive Events														
Step 1														
BDI	0.03	0.02	4.31	**.04**	1.03	1.00	1.05	0.02	0.02	1.77	.18	1.02	0.99	1.05
HMI	0.01	0.02	0.32	.57	1.01	0.98	1.05	0.05	0.02	6.57	**.01**	1.05	1.01	1.08
Step 2														
BDI	0.03	0.01	4.23	**.04**	1.03	1.00	1.06	0.02	0.02	1.87	.17	1.02	0.99	1.05
HMI	0.01	0.02	0.31	.57	1.01	0.98	1.05	0.05	0.02	6.15	**.01**	1.05	1.00	1.09
Episodes	0.02	0.02	1.10	.29	1.02	0.98	1.06	<0.01	<0.01	1.32	.25	1.00	1.00	1.00
Minor Positive Events	1.46	0.93	2.48	.11	4.31	0.70	26.50	3.46	0.87	15.79	**<.01**	31.70	5.76	174.32
Step 3														

	Prospective Depression							Prospective (Hypo)mania						
						95% CI							95% CI	
Predictor	**B**	**S.E. B**	**Wald**	***P***	**OR**	**Lower**	**Upper**	**B**	**S.E. B**	**Wald**	***P***	**OR**	**Lower**	**Upper**
BDI	0.03	0.01	3.45	.06	1.03	1.00	1.06	0.02	0.02	1.76	.18	1.02	0.99	1.05
HMI	0.01	0.02	0.41	.52	1.01	0.97	1.05	0.05	0.02	6.10	**.01**	1.04	1.01	1.09
Episodes	>−0.01	0.03	0.01	.94	1.00	0.95	1.05	<0.01	<0.01	0.24	.63	1.00	1.00	1.01
Minor Positive Events	−1.98	3.18	0.39	.53	0.14	<0.01	70.26	3.50	0.91	14.80	**<.01**	32.94	5.55	195.49
Episodes x Minor Pos. Events	0.38	0.33	1.30	.25	1.46	0.76	2.80	>−0.01	0.01	0.02	.88	1.00	0.97	1.03

Note. BDI = Mean Beck Depression Inventory score from baseline to first onset of episode or end of study; HMI = Mean Halberstadt Mania Inventory score from baseline to first onset of episode or end of study.