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Kindling of Life Stress in Bipolar Disorder: Effects of Early Adversity

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Most theoretical frameworks regarding the role of life stress in bipolar disorders (BD) do not incorporate the possibility of a changing relationship between psychosocial context and episode initiation across the course of the disorder. The kindling hypothesis theorizes that over the longitudinal course of recurrent affective disorders, the relationship between major life stressors and episode initiation declines (Post, 1992). The present study aimed to test an extension of the kindling hypothesis in BD by examining the effect of early life adversity on the relationship between proximal life events and prospectively assessed mood episodes. Data from 145 bipolar participants (59.3% female, 75.2% Caucasian, and mean age of 20.19 years; *SD* = 1.75 years) were collected as part of the Temple-Wisconsin Longitudinal Investigation of Bipolar Spectrum Project (112 Bipolar II; 33 Cyclothymic disorder). Participants completed a self-report measure of early adversity at baseline and interview-assessed mood episodes and life events at regular 4-month follow-ups. Results indicate that early childhood adversity sensitized bipolar participants to the effects of recent stressors only for depressive episodes and not hypomanic episodes within BD. This was particularly the case with minor negative events. The current study extends prior research examining the kindling model in BD using a methodologically rigorous assessment of life stressors and mood episode occurrence. Clinicians should assess experiences

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of early adversity in individuals with BD as it may impact reactivity to developing depressive episodes in response to future stressors.

Keywords: bipolar disorder; kindling; childhood adversity; stress

BIPOLAR DISORDERS (BD) affect an estimated 2%–4% of the U.S. population and are the sixth leading cause of disability among physical and psychological disorders worldwide (Miklowitz & Johnson, 2009; Murray & Lopez, 1996). Research examining the impact of life events on symptom expression, timing, and severity of affective episodes in BD has been especially promising in elucidating the etiology and course of these disorders. 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, 2005). However, most of this literature does not take into account the possibility of a shifting relationship between psychosocial context and episode initiation across the course of BD.

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. Based on this model, Post asserted that life stressors may leave long-term vulnerabilities, thereby lowering the threshold of stress exposure required for episode recurrence, so that, over time, relatively minor stressors may trigger a mood episode. In examining the evidence relevant to the kindling model, Post reviewed eight studies on unipolar depression (UD), six on BD, and two on both UD and BD and found support for the notion that major psychosocial stressors play a more important role in initial affective episodes than in recurrences. Later researchers have hypothesized two separate processes through which the relationship between stressors and mood episodes is reduced over time, namely the stress sensitization and the stress autonomy models (Monroe & Harkness, 2005). The *stress sensitization* model suggests that individuals become increasingly sensitized to stressful events such that stressors that may not have been severe enough to trigger an initial mood episode onset would later be able to trigger a recurrent episode. One way to examine whether the threshold for a mood episode is lower is to assess the number of stressors that precede its onset. In this way, individuals who are sensitized would experience a greater frequency of minor events but a lower frequency of major events prior to new recurrent episodes, and increased impact of both minor and major events before a new episode (see Monroe & Harkness, 2005, p. 428, for a descriptive figure). Whereas both major and minor stressors would trigger recurrent mood episodes, the frequency of minor events would be more likely to elicit a new episode over time. That is, prior mood episodes do not cause fewer events to occur before a new mood episode onset; rather, higher numbers of previous episodes lower the threshold for new episodes, so that episodes occur sooner. In contrast, the *stress autonomy* model suggests that subsequent mood episodes will be less tied to input from the environment, and thus, both major and minor stressors would become less associated with progressive episodes over time (Monroe & Harkness, 2005).

THE KINDLING HYPOTHESIS IN BIPOLAR DISORDER

A recent review examined the literature focused on testing the kindling hypothesis in BD and found inconsistent support (see Bender & Alloy, 2011, for a detailed review). Early studies used cross-sectional designs comparing rates of life events in patients experiencing a first episode versus a recurrence (Ambelas, 1979, 1987; Perris, 1984) or retrospective designs that examined the frequency of life events occurring prior to participants' earlier vs. later episodes (Bidzinska, 1984; Dunner et al., 1979; Ehnvall & Ågren, 2002; Johnson et al., 2000) with some not finding support for a kindling effect in BD (Glassner & Haldipur, 1983; Kennedy et al., 1983). These mixed findings were attributed to long intervals for recall and the use of stress checklists that may be biased by participants' current mood or fallible memory. To address these limitations, Hammen and colleagues conducted three prospective studies that used shorter recall intervals (e.g., 3 months in contrast with more than 10 years in some retrospective studies) and life stress interviews to examine negative events instead of stress-checklists (Dienes et al., 2006; Hammen & Gitlin, 1997; Swendsen et al., 1995). However, Hammen and colleagues did not interpret their findings in these three studies to be consistent with a kindling effect. Although methodologically more advanced than prior studies, these three studies did not distinguish between major and minor life events and did not differentiate between episodes of different polarities, and thus, could not differentiate between the sensitization or autonomy models of kindling (Bender & Alloy, 2011).

A recent study by Weiss and colleagues (2015) aimed to address limitations of these previous studies. Similar to the Hammen studies, Weiss et al. used contextual threat interviews to assess life events in order to reduce reporter bias as well as

relatively short time intervals to help accurately date life events. In addition, this study advanced knowledge of the kindling effect by examining polarity-specific hypotheses (i.e., negative life events predicting depressive episodes and positive life events predicting [hypo]manic episodes), reporting that the valence of the event (negative or positive) determined which type of mood episode (depressive or [hypo]-manic) occurred (Weiss et al.). This study found support for the kindling hypothesis in BD, and more specifically for the sensitization model indexed by individuals with more prior mood episodes having a higher number of minor negative events preceding depressive episodes and of minor positive events before hypomanic episodes, indicating that the threshold for prospective mood episodes was lower.

As with UD kindling research, the majority of BD kindling studies have focused on analyses of life events frequency, while fewer have examined the issue of life events *impact*. Life events indices have varied across studies, and only one other study (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 whether minor stressors elicit a mood episode in place of more severe life stressors, a finding that would be consistent with the kindling hypothesis and differentiate between the sensitization and autonomy models of kindling. In summary, support for Post's (1992) kindling model of BD has been inconsistent because of the challenging and nuanced manner of measuring and conceptualizing life stress; however, recent studies have attempted to address these hurdles by taking a fine-grained approach.

EARLY CHILDHOOD ADVERSITY

Childhood adversity, such as prolonged parental separation or neglect, physical abuse, or sexual abuse, is generally considered distinct from recent life events (Grandin et al., 2006). The early adversity sensitization (EAS) hypothesis contends that these adverse childhood experiences result in lasting alterations in the stress response system. Specifically, the EAS hypothesis asserts that the alterations initiated by distal early stressors compromise homeostatic processes in the context of recent, more proximal stressors (e.g., recent divorce or job loss). As in the stress sensitization hypothesis, this model contends that increased vulnerability to ongoing life stress (activated by early adversity) lowers the threshold required to trigger affective episodes, leading to a more pernicious course of BD (Post et al., 2001). The idea that sensitization occurs as a function of early adversity helps to provide insight not only into the longitudinal course of mood disorders, but also into potential distal etiological factors (Harkness et al., 2006).

Human and animal research supports the idea that early adversity has lasting effects on the stress response system. In a number of animal species, early life stressors can alter brain growth, pruning, and responsiveness to learning and memory processes (Post et al., 2001), which influences stress and behavioral response patterns over the life span (Heim et al., 2008). An EAS effect also has been demonstrated in unipolar depressed and anxious samples. For example, Hammen and colleagues (2000) examined a number of childhood adversities and found a stress-sensitization effect in which women with higher levels of early adversity showed more depressive reactions to low levels of recent stressors compared to those with fewer adversities. Kendler and colleagues (Kendler et al., 2004) found that childhood sexual abuse conferred an overall increased risk for major depression, as well as an increased sensitivity to the depressogenic effects of recent life stressors.

Surprisingly, few studies have examined the EAS hypothesis in BD, and the extent to which the above findings translate to bipolar samples is unclear. Cross-sectional studies show elevated rates of early adversity among bipolar samples (e.g., Grandin et al., 2007), and there is support for the idea that early adversity contributes unique variance to a worse course of bipolar disorder (e.g., Brown et al., 2005). Using a self-report questionnaire of life stress, Leverich and colleagues (2002) found that participants with early adversity had higher rates of stressful life events prior to both their initial and most recent episodes. Results were interpreted as reflective of an EAS process; however, an EAS phenomenon in the context of a kindling model would be reflected in an increased sensitivity to *lower* number/severity of life stressors prior to subsequent episode onset. The one existing study to examine EAS using interview methods of childhood adversity and recent life events provided support for the hypothesis in 58 patients with Bipolar I disorder (Dienes et al., 2006). Using a prospective longitudinal design, Dienes and colleagues found that childhood stress interacted with recent life events, such that those with severe early adversity evidenced a higher likelihood of relapse when exposed to mild recent stressors than individuals with mild or no early adversity.

THE PRESENT STUDY

The present study aimed to examine the kindling effect of early childhood adversity in BD in the context of sensitization and autonomy models. To properly test these models, it is necessary to independently examine the frequency (the probability of an

antecedent stressor, given the occurrence of an episode) and the impact of stressors (the probability of a subsequent episode, given the occurrence of a stressful event). Importantly, because studies on acute mood episodes of BD have found specificity in the prediction from life events to depressive vs. (hypo)-manic episodes (Alloy et al., 2005; Johnson, 2005; Johnson et al., 2008), polarity-specific analyses were conducted in examining the kindling effect of early adversity in the current study. Using a fine-tuned approach consistent with recent investigations (Weiss et al., 2015), we hypothesized relationships between early adversity, proximal life stressors, and mood episodes that would be consistent with an EAS model of *stress sensitization* in BD as opposed to the autonomy model. Specifically, we predicted that as the number of early life stressors increases, the number of recent life events preceding a mood episode would decrease in number but increase in impact. In line with the sensitization model (Monroe & Harkness, 2005, p. 429), we hypothesized that as early life stressors increase, both major and minor recent events would increase in impact; however, the frequency of major events preceding a new episode would be lower whereas the frequency of preceding minor events should be greater. That is, early life stress does not cause fewer events to occur; rather, it lowers the threshold so that episodes occur sooner as indexed by relative reductions in frequency of major events compared to minor events. In addition, we hypothesized polarity specificity such that the sensitization relationship between a history of childhood adversity, recent events, and new prospective depressive episodes would hold for negative events, but not for positive events, whereas the relationship between a history of childhood adversity, recent events, and new prospective (hypo)manic episodes would hold for positive events, but not for negative events.

Methods

PARTICIPANTS AND PROCEDURE

Participants were drawn from a two-site longitudinal investigation of the predictors of the course of BD, the Temple-Wisconsin Longitudinal Investigation of Bipolar Spectrum Project (LIBS) Project (see Alloy et al., 2008, 2012). Both sites' institutional review boards approved this study. A two-phase screening process was implemented to select participants for the LIBS project. In Phase I, a revised General Behavior Inventory (GBI; Depue et al., 1989) was administered to approximately 20,500 university students. Depue et al. (1989) recommend the use of a case-scoring method to identify potential BD and control participants, which was validated against diagnoses derived from SADS-L interviews (Alloy et al., 2008, 2012). Participants who met GBI screening criteria (see measures section) were considered potentially eligible to be assigned to either the BD or control group. These participants were invited to complete Phase II screening, in which they were administered a semistructured diagnostic interview (see measures).

Participants meeting the high GBI cutoff who met *Diagnostic and Statistical Manual for Mental Disorders* (*DSM-IV*; American Psychiatric Association, 1994) criteria or Research Diagnostic Criteria (RDC; Spitzer et al., 1978) for bipolar II disorder, cyclothymic disorder, or bipolar disorder not otherwise specified (BD-NOS) were considered eligible to participate in the longitudinal portion of the LIBS project, and were assigned to the BD group. Expanded criteria including the *DSM-IV* and RDC were used to enable greater accuracy and reliability in diagnosis of bipolar conditions and expert consultation was used to ensure clinical validity of the diagnostic procedures (see Alloy et al., 2008, 2012 for more details). Exclusion criteria included experiencing at least one full-criteria manic episode prior to study onset, given that the LIBS project was designed in part to investigate predictors of the progression to bipolar I disorder. Control group participants were not included in the current study sample, as we were solely interested in understanding the kindling effect in individuals with BD.

The final study sample included 227 BD participants, who were not significantly different from the originally screened 20,500 students in regards to gender, $\chi^2(1) = 1.21$, $p = .27$, age, $t(441) = -0.73$, $p = .46$, or ethnicity, $\chi^2(5) = 9.26$, $p = .10$. Thus, the sample utilized in the present study can be considered representative of the larger LIBS project sample. The BD group was 59.2% female, 68.5% Caucasian, and participants were 20.06 years old at the start of the study ($SD = 1.75$ years). At an initial Time 1 assessment, participants completed a variety of measures and subsequently completed regular prospective assessments at 4-month intervals for an average of 38.1 months ($SD = 19.1$). Diagnostic interviews (Schedule for Affective Disorders and Schizophrenia–Change Version; Endicott & Spitzer, 1978) were administered at each prospective assessment in order to be able to document comprehensive information on timing, severity, and duration of mood episodes occurring since the previous assessment. Additionally, at each prospective assessment, an independent interviewer, who was blind to the participant's lifetime and concurrent diagnoses and group status, administered both a self-report Life Events Scale and the Life Events Interview (LES and LEI; Alloy & Clements, 1992; Francis-Raniere et al., 2006; Needles & Abramson, 1990) in order to collect details about timing, severity, and contextual

factors of psychosocial events that occurred since the previous assessment of life events. Prior to entering the study, all participants provided written, informed consent. Participants were reimbursed for their time.

The present study was based on data from all BD-group participants who had complete data for study variables of interest (i.e., lifetime history of mood episodes, prospectively assessed mood episodes, prospective life events, and early adversity). The total number of participants was 145 (112 Bipolar II; 33 Cyclothymic disorder) and included 59.3% females, 75.2% Caucasians, and they were 20.19 years old at the start of the study (SD = 1.75). Participants in the current study did not differ from the larger BD group based on age, gender, or number of early adverse life events. Participants in the current study were more likely to be Caucasian, $t(221) = 2.22$, $p = .027$, participated longer in the study, $t(221) = 2.79$, $p < .01$, were more likely to have Bipolar II than Cyclothymic disorder, $t(221) = 1.97$, $p = .05$, and experienced more mood episodes, $t(221) = 4.51$, $p < .01$, than the larger group of bipolar participants.

MEASURES

Screening at Phase I and II

General Behavior Inventory. The revised General Behavior Inventory (GBI; Depue et al., 1989) is a self-report questionnaire utilized during the Phase I screening that 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*). Participants whose GBI-D scores exceeded 11 and GBI-HB scores exceeded 13, using the case-scoring method in which responses of a 3 or 4 count as a point, were considered to be potential bipolar participants (see Alloy et al., 2008). The psychometric properties of the revised GBI are strong, with internal consistency of α's = .90 to .96, test-retest reliability of r's = .71 to .74, adequate sensitivity (.78), and excellent specificity (.99) for bipolar spectrum disorders (Depue et al., 1989; Depue et al., 1981; Mallon, Klein, Bornstein, & Slater, 1986). The GBI has been psychometrically validated as a first-stage case identification procedure for BD among a range of populations (Alloy et al., 2008; Depue et al., 1989; Depue et al., 1981; Klein et al., 1985; Mallon et al., 1986). In the LIBS Project Phase II sample, the GBI had α's = .95 and .87 for the Depression and Hypomania/Biphasic scales, respectively.

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) semistructured 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. The exp-SADS-L interview has evidenced good interrater reliability for diagnoses of major depressive episodes (k's > .95) and all UD diagnoses (k's > .90) (Alloy et al., 2000), and for bipolar diagnoses (k's > .96) in the current study based on 105 jointly rated SADS-L interviews (Alloy et al., 2008).

Criteria for bipolar disorders. Lifetime bipolar disorders were diagnosed according to *DSM-IV* and RDC criteria. 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 the 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 2-year period; the periods of affective disturbance could not meet criteria for major depressive or manic episodes. To receive a diagnosis of cyclothymic disorder, participants must not have been free of symptoms for more than 2 months over the 2-year period.

Longitudinal Mood Episodes

The Expanded SADS-Change (SADS-C; Endicott & Spitzer, 1978). The SADS-C was used to assess the timing, duration, and severity of prospective mood episodes at each 4-month follow-up interval. It was expanded in the same way as the SADS-L and allowed diagnosis of *DSM–IV* and RDC mood episodes. Interviewers were blind to participants' prior diagnoses and group status and used features of the Longitudinal Interval Follow-up Evaluation (LIFE II; Shapiro & Keller, 1979) to facilitate accurate recall of the timing of symptoms and episodes. The expanded SADS-C has demonstrated good interrater reliability and validity data for the occurrence and dating of

symptoms (Francis-Raniere et al., 2006). Interrater reliability for the SADS-C in joint ratings of 60 interviews from the LIBS Project was good ($k > .80$; Francis-Raniere et al.). In addition, in a validity study, participants dated their symptoms on the SADS-C with at least 70% accuracy compared with daily symptom ratings made over a 4-month interval (Francis-Raniere et al.).

Criteria for prospective affective 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 4 days for *DSM-IV* and 2 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 also were 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 2 weeks). 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.

Longitudinal Self-Reported Mood 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 (Beck et al., 1988). 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 (hypo)-manic 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 (Alloy et al., 2008), were correlated with hypomanic symptoms rated in the SADS interview ($r = .46$), and had an internal consistency of $\alpha = .78$ in the LIBS Project (Alloy et al., 2008). LIBS project participants completed a BDI and HMI at each regular prospective assessment, and were asked to provide separate responses for each 1-month period elapsed since the previous follow-up. In the present study, BDI and HMI scores were included as covariates to control for subsyndromal depressive or hypomanic symptoms that may have impacted pre-episode event rates.

Life Events

The assessment of life events in the current study was carried out in a two-phase process using a contextual threat based approach (Brown & Harris, 1978). First, participants were administered a self-report Expanded Life Events Scale (exp-LES; Francis-Raniere et al., 2006). Next, participants were administered an interview, the Life Events Interview (LEI), conducted by trained postdoctoral fellows, doctoral-level students, MAs in clinical psychology, and post-BA salaried research assistants unaware of participants' diagnostic status. The exp-LES and LEI were given at every follow-up.

Life Events Scale. The version of the LES employed in the LIBS project (Francis-Raniere et al., 2006) 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 in the inventory was carefully designed to reduce vagueness and to prevent repetitiveness. Furthermore, items were removed from the inventory if they directly reflected affective symptomatology (e.g., "Had a significant emotional problem or trauma that lasted at least 2 weeks"). Participants were asked to report whether an event occurred since the last assessment. Each event was *a priori* categorized by the consensus team (composed of four doctoral students with extensive training on the LEI methods and the PI) to determine its valence (negative/positive) and severity (major/minor). The severity was rated on a 4-point scale ranging from 0 (*no/slight*) to 4 (*extreme*), indicating the degree it would affect an average individual in average circumstances. Events with an average score of 3 or more were categorized as major and those with average ratings

of 2 or lower were categorized as minor (Weiss et al., 2015). 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 et al., 2007). For example, test-retest reliability over a period of 3 weeks was .82 (Saxe & Abramson, 1987).

Life Events Interview. Following completion of the LES, participants completed a Life Events Interview (LEI; Francis-Raniere et al., 2006) with interviewers who were blind to group membership, and symptoms and diagnoses. The LEI functioned to improve both the reliability and the validity of the events reported by participants on the LES. Furthermore, the LEI also facilitated precise dating of event onsets and offsets to ensure that the event occurred within the appropriate time period. Employing both the LES and the LEI in tandem guards against many of the validity issues exhibited in other life stress studies (see Johnson, 2005). For example, reporting biases that may result due to affective state are reduced by exclusion of events that do not meet the rigorous and objective a priori determined criteria for each event. The LES has demonstrated good interrater reliability and dating of events (Alloy & Abramson, 1999; see also Safford et al., 2007). 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 interrater reliability study based on 40 LEIs yielded an $r = .89$ for the dating of events (Alloy & Abramson, 1999; Safford et al., 2007). In a validity 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 1 day with 92% accuracy, and minor events were dated to within 1 day with 80% accuracy (Francis-Raniere et al., 2006).

Taken together, these results suggest a relatively high degree of reliability and validity 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. The results also 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.

Early adversity. The Children's Life Events Scale (CLES; Crossfield, Alloy, Gibb, & Abramson, 2002) is a checklist of 50 negative events of moderate to major severity that children may experience in their lifetime, expanded from the Source of Stress Inventory (Chandler, 1981). For example, items ask whether the participant experienced "severe illness requiring hospitalization of parent," "parental divorce," "experiences of physical abuse," and "overcrowding with living space." Participants retrospectively completed the CLES and indicated when these events occurred. The current study only used events prior to the earliest onset of disorder. These items were summed with a mean of 6.90 events and scores ranging from 0 to 40, with higher scores indicating more experiences of early childhood adversity. Several studies have demonstrated predictive validity of the CLES (e.g., Crossfield et al., 2002; Grandin et al., 2007) and consistency in the total number of negative childhood life events reported by children and their parents, $r = .61$, $p < .01$ (Chandler, 1981).

DATA ANALYTIC PLAN

We tested the kindling hypothesis in two primary ways, consistent with previous prospective research on kindling in BD (Weiss et al., 2015). First, to evaluate the *frequency* component, we used hierarchical linear regression to examine whether the number of early life stressors significantly predicted the frequency of events in the 30 days preceding the first prospective episode of depression or hypomania. Therefore, the independent variable was the number of early life stressors and the dependent variable was the number of life events preceding a mood episode. To demonstrate a sensitization effect, we hypothesized that higher levels of childhood adversity would prospectively predict fewer events during the 30-day pre-episode period. Analyses were conducted to determine whether this effect was polarity specific, examining the frequency of negative events preceding depressive episodes in those with high childhood adversity as opposed to positive events, and vice versa for hypo/manic episodes. Follow-up analyses were conducted separately for major and minor events. The sensitization model suggests that major events should be fewer in number, whereas minor stressors should be greater in number prior to a mood episode as childhood adversity increases, thereby changing the threshold for the number of events needed to trigger an episode.

The first step of the model controlled for the number of lifetime mood episodes so as to examine the specific effects of early adversity. For all models, the following covariates also were considered for

inclusion: BDI and HMI scores during the 30-day period prior to the episode; age at study entry; and age at initial episode onset, as relevant. Only BDI/HMI scores were significant in the models; however, upon further testing, including these as covariates did not change the outcome of analyses and would be too closely related to the outcomes of interest, and thus, were dropped from the final model. 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 also were considered for inclusion in the model. These were either nonsignificant in the regression models or did not change the outcome of the analyses.

Second, we conducted a series of survival analyses using Cox proportional hazard regressions (Lenze et al., 2008; Tabachnick & Fidell, 2007) to evaluate whether the *impact* of life events on the time until the prospective onset of the mood episode differed based on the number of early life stressors. That is, life events were summed from the start of the study until the first prospective episode by combining the 4-month interval event scores. This examination focused on the interaction between early life adversity and proximal life stressors to predict new prospective episodes with similar polarity specific hypotheses. The first step in these analyses contained symptoms of either depression or hypomania across the follow-up period prior to the onset of a mood episode. The second step contained the main effect of the number of early adverse events and the number of proximal stressful events preceding the episode. Only events occurring before the onset of the first prospective mood episode were included for the main event variable. The final step included the main predictor of the interaction between proximal life stressors and the number of early life adverse events. The interaction term was computed in the regression as the product between early adverse events and the number of recent stressful life events. Consistent with the sensitization model, we hypothesized that the number of early adverse events would moderate the effect of recent events on the time to an episode recurrence, such that the impact of major and minor events would increase as the number of early adverse events increases.

Results

DEMOGRAPHIC CHARACTERISTICS AND ASSOCIATIONS AMONG STUDY VARIABLES

There were no gender differences in number of adverse early life events, $t(199) = -0.69$, $p = .49$, negative, $t(117) = .47$, $p = .64$, or positive events, $t(117) = -0.59$, $p = .55$, prior to a depressive episode, or negative, $t(109) = .26$, $p = .79$, or positive events, $t(109) = -1.26$, $p = .21$, prior to a (hypo)manic episode. Age and race were not correlated with the outcome measures of events prior to a depressive or (hypo)manic episode or experiences of adverse life events.

KINDLING: TEST OF FREQUENCY OF LIFE EVENTS

Table 1 presents results of four multiple linear regression analyses examining the relationship between early adversity and 30-day sums of life events prior to prospectively assessed depressive or (hypo)manic episodes. As seen in Table 1, regression models were run separately for negative and positive proximal stressors prior to either a depressive episode or (hypo)manic episode to test the specificity of our model and to further assess the polarity of effects in the sensitization model. Consistent with the kindling hypothesis, individuals with greater early childhood adversity had fewer negative events prior to a depressive episode ($B = -.38$, $t = 2.68$, $p = .008$). However, results did not support an association

Table 1
Polarity Specific Regression Analyses Examining the Kindling Hypothesis in BSD

	Number of Events Prior to a Depressive Episode					Number of Events Prior to a Hypomanic Episode				
Predictors	*B*	S.E.	β	*t*	ΔR^2	*B*	S.E.	β	*t*	ΔR^2
Negative Events										
Lifetime Episode	0.08	0.07	0.10	1.22	.003	0.12	0.05	0.24	2.52*	.055
Early Life Stress	-.38	0.14	-.22	2.68**	.047	0.15	0.16	0.09	0.94	.088
Positive Events										
Lifetime Episode	0.04	0.05	0.07	0.86	.006	0.04	0.04	0.11	1.08	.009
Early Life Stress	0.01	0.09	0.01	0.13	.000	0.12	0.12	0.10	1.00	.010

* $p < .05$, ** $p < .01$; Lifetime Episode corresponds to the predicted episode and was entered as a covariate in step 1.

between early childhood adversity and fewer recent positive stressful events prior to a (hypo)manic episode (B = .12, t = 1.00, p = .32). As expected, negative events were not associated with (hypo)manic episodes and positive events were not associated with depressive episodes.

Follow-up analyses then were run to examine whether the severity of the recent stressors affected the association between early adversity and the number of negative events prior to a depressive episode. As before, linear regression analyses were conducted controlling for number of lifetime episodes prior to the study. Results indicated that early childhood adversity was not significantly associated with the number of major negative events prior to a depressive episode (B = -.004, t = .18, p = .85). However, individuals with greater early childhood adversity had fewer minor negative stressors prior to a depressive episode (B = -.36, t = 2.01, p = .046). Thus, the severity of the stressors may impact the kindling effects of early adversity.[1]

KINDLING: TEST OF IMPACT OF LIFE EVENTS

Cox regression analyses examined the relationship between early life adversity and the time from the beginning of the study to the prospective onset of a new episode. In line with a stress sensitization model, we hypothesized that the number of early adverse life events would moderate the effect of proximal events on the time to episode recurrence, such that the impact of proximal life events would increase as the number of early life adverse events increased. Therefore, the main predictor of interest was the interaction between the number of early life adverse events and the number of life events before the prospective onset of a mood episode that were polarity specific. Counter to hypotheses, the number of early life adverse events did not interact with any proximal life events to predict the time to onset of prospective depressive episodes or the time to onset of prospective (hypo)manic episodes, providing no support for the impact hypothesis of the kindling model in BD.

Discussion

The goal of the current study was to examine whether early adversity plays a role in the process of sensitization to stress in BD, in line with the kindling hypothesis, and more specifically, the sensitization model. A growing body of evidence suggests that early childhood adversity (i.e., distal stressors) may have causal implications for stress reactivity and psychopathology across the lifespan (Dienes et al., 2006; Grandin et al., 2007; Heim et al., 2008; Leverich et al., 2002; Post et al., 2001). The current study found partial support for a sensitization effect of early childhood adversity that was specific to depressive episodes within BD. A dearth of research has examined polarity specific sensitization effects within BD. Findings suggest that even though bipolar disorder involves periods of depression and (hypo)mania, early childhood adversity, as it applies to the kindling hypothesis, may be specific only to the depressive pole. More research directly examining the kindling effect in BD is needed to have more confidence in this claim, but the current findings suggest that early life stress, as a distal environmental contributor to stress sensitization, is an important factor in the course of BD.

The current study results are partially consistent with our hypothesis that early adversity would contribute to sensitization, thereby supporting a kindling effect. Additionally, as hypothesized, positive events did not differentially predict depressive episodes. As research on the kindling hypothesis is based on models focused on unipolar depression, much is still unknown about this process in BD. Findings from the current study indicated that early-life adversity did not alter the relationship between the number of recent stressors and the onset of (hypo)mania. This suggests that the sensitization effects of early adversity may be depression-specific, but only in terms of the frequency component of the stress sensitization model. Importantly, research shows that early adversity may be an important predictor of BDs and may predict a worse course of the disorder.

Several of the hypotheses were not supported in the current study, however. Findings did not support the *impact* component of the sensitization model for either depressive or (hypo)manic episodes. That is, the increased probability of a subsequent episode given the occurrence of a recent stressful event was not supported, suggesting that an accumulation of events may not differentially increase the likelihood of an episode based on early adversity. Analyses of the impact component examined the moderating effect of early adverse experiences on an accumulation of stressors since the start of the study. The presumption of this test is that experiences of stressors are additive in nature over a long period. A contrasting perspective could argue that the relative importance of these events

[1] Consistent with prior literature, the residuals of early life stress (CLES) were positively skewed. To test whether this impacted the results, we conducted analyses with a more normally distributed log transformed CLES. The results were consistent whether we used this transformed variable or the nontransformed CLES. Given that much prior research has not transformed measures of early life stress and the difficulty in interpreting log transformed variables, we chose to retain the original CLES in analyses.

may diminish if they occurred far earlier than the episode onset and that the stressful life events that are more proximal are of increased importance. The Monroe and Harkness (2005) model suggests that the frequency of major stressors should decrease and that the frequency of minor stressors should increase prior to a mood episode as early adversity increases. Our findings indicated that the frequency of minor stressors decreased prior to an episode. Although the frequency of minor stressors was significantly lower, the impact of these events may be increased for depressive episodes during the preceding month, and thus, may be suggestive of a sensitizing effect. Overall, the pattern of the effects of early adversity in sensitizing individuals with BD to mood episodes following recent stressors was modest and provided only partial support. The current study findings suggest that environmental input continues to be associated with episode occurrences, and thus, did not provide support for a stress autonomy model.

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 3 years. Assessments of mood episodes were interview-based, which produces reliable data that is considered the standard in the field (Miller, Johnson, & Eisner, 2009). 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 thus were 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. Also, the present study utilized carefully defined categories of event severity and a polarity-specific approach to testing the kindling hypothesis. It is important to note the decision to use a common window of 30 days preceding a mood episode to measure recent life events. This was done to have a comparatively recent time-frame to assess different numbers of events as a function of experiences of early adversity consistent with recent studies examining kindling in BD (Weiss et al., 2015). However, this is different than the conceptualization of measuring the accumulation of life stressors during an inter-episode period that could also be interpreted as a test of the kindling model. Therefore, interpretation of the current findings should take this decision into account.

Although this study had a number of strengths, findings should be interpreted keeping its limitations in mind. Sample generalizability should be considered carefully. The final sample was biased towards bipolar participants who experienced episodes within the follow-up window and did not include individuals diagnosed with bipolar I. Previous research on kindling in bipolar disorder has focused primarily on individuals with bipolar I disorder. Although use of a mostly bipolar II sample in the current study represents a novel contribution to the literature, it is also possible that kindling may present differently at the higher ends of the spectrum of episode severity. Participants did not experience enough severe hypomanic or full-blown manic episodes to examine whether kindling operates differently based on the severity of the mood episode. Also, the sample was comprised of bipolar participants who already had experienced the first onset of the disorder. 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). In addition, the measure of early life stress was a retrospective assessment of childhood adverse events. Although this measure is similar to other commonly used event checklists (Bernstein & Fink, 1998; Felitti et al., 1998), the measurement of childhood events may be subject to reporter biases associated with memory or mood. Thus, findings should take into account the methodological drawback of retrospective report and future studies may employ interview-based methods similar to the LES/LEI procedure or other early-life adversity interviews. Similarly, we chose to count childhood adverse life events up until participants' earliest age of onset of a mood disorder to disentangle effects of mood episodes from events. However, as a function of this decision, it may be the case that those with later initial onset of mood episodes had the opportunity to have more adverse events and this may have skewed the findings. Finally, it would be important to include measurement of chronic stressors in future studies to understand the role of more persistent stress that may reduce the threshold for episodes of depression or mania. In order to most precisely examine the kindling hypothesis in relation to early adversity, enrolling teens at high and low risk for disorder onset and following these participants

for multiple years would allow us to best understand the relationship between early stress and *initial onset* of BD, as well as between early stress and subsequent affective episodes. Such a design would allow us to most sensitively test differential impact of stressors over the course of the disorder.

The current study's results have several important clinical implications. First, it may be important for clinicians to assess experiences of early-life adversity, even after initial diagnosis of BD is made, as it may play a role in determining the depressive course of the disorder. That is, as the course of the disorder advances, individuals with high early-life stress may be progressively vulnerable to depressive episode relapse when encountering even minor stressors.

The vast majority of psychological treatment modalities intend to teach clients to respond to stressors in more adaptive ways, as to minimize symptom activation. The current study suggests that even responses to minor events may be important to target in therapy for individuals who have a history of early adversity. With the knowledge that BD patients with early adversity may be particularly vulnerable to even minor stress, clinicians may be equipped to preemptively minimize precipitants of depressive episodes. Both problem-focused and emotion-focused coping skills (Mazure, 1998) may aid in the reduction of overall stress levels, thereby serving as potentially important resiliency factors. Coping strategies designed to help clients anticipate stressors and proactively prepare for their management may be particularly helpful (Post, 2007). 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.

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., reward-relevant events, social rhythm disruption events) represents one way of approaching this task. The effect of early childhood adversity may operate through neurobiological changes involving the HPA axis and cortisol regulation (Heim et al., 2008; Kendler et al., 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. Multitrait and multimethod assessments will be critical in the examination of a process that is hypothesized to occur on multiple levels of analysis.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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