

Life events in bipolar disorder: Towards more specific models

Sheri L. Johnson

University of Miami, United States

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Abstract

This article reviews the evidence concerning life events as a predictor of symptoms within bipolar disorder. First, key methodological issues in this area are described, and criteria used for including studies in this review are defined. Then findings that negative life events predict worse outcomes within bipolar disorder are reviewed. Beyond general studies on relapse, it is important to differentiate predictors of depression from predictors of mania. When severe negative life events occur, they appear to trigger increases in bipolar depression. Nonetheless, many depressions are unrelated to negative life events and appear to be triggered by other variables. The strongest evidence suggests that negative life events do not trigger mania, except perhaps in certain contexts. Retrospective findings for schedule-disrupting life events as a trigger for manic symptoms await further assessment within a longitudinal study. Life events involving goal attainment do appear to trigger manic symptoms. Overall, it is time to differentiate among specific types of life events, as these different forms of events point towards mechanisms linking stressors with symptom expression. These mechanisms provide clues into ways to integrate the social environment with biological vulnerability (see [Monroe, S. M., & Johnson, S. L. (1990). *The dimensions of life stress and the specificity of disorder*. *Journal of Applied Social Psychology*, 20, 167–1694; Harris, T. O. (1991). *Life stress and illness: The question of specificity*. *Annals of Behavioral Medicine*, 13, 211–219]).

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Bipolar disorder is clearly a biological disorder. Nonetheless, over the past 15 years, a wealth of research has made it abundantly clear that psychosocial variables shape outcomes of this disorder. Much of this psychosocial research has focused on whether life events predict the timing and severity of symptoms within this disorder.

E-mail address: Sjohnson@miami.edu.

This paper reviews the evidence that life events are related to symptom expression within bipolar disorder. This basic question has challenged researchers for over 20 years. Given the growing literature, this paper focus on addressing two more specific questions. Which types of symptoms are related to life events? What types of life events influence symptoms? Given the growing number of studies available on these issues, this review will focus on those studies with the most rigorous methodologies. To set the stage for this endeavor, it is important to first review the major methodological issues in research on life events and bipolar disorder, including issues related to design, measurement, and sampling.

1. Design issues in studies of life events and bipolar disorder

Researchers have used many different designs in this field, both cross-sectional and longitudinal. There are genuine difficulties in interpreting the results of cross-sectional studies. Consider that some people with bipolar disorder experience elevated levels of life stress even during asymptomatic periods. High rates of divorce (Kessler, Walters, & Forthofer, 1998), unemployment (Goldberg, Harrow, & Grossman, 1995), victimization (Goodman et al., 2001), and stigmatization (Hayward, Wong, Bright, & Lam, 2002; Torrey, 2002) are well-documented in this population. Given these sad consequences of disorder, it should not be hard to document high levels of stress at any time in the lives of people with bipolar disorder compared to people with no mental illness—cross-sectional findings could overestimate the role of life events as triggers of symptoms in bipolar disorder, because these designs do not provide information about whether life events are specifically elevated before episodes of bipolar disorder as compared to other times in the lives of people with bipolar disorder.

Between-group comparisons, then, do not address a key question—are episodes preceded by increases in stress? That is, researchers can assess whether life events are more common before episodes than they are after episodes. This contrast between time periods provides tighter control than the between-group comparisons described above.

Others have considered a slightly more powerful question. When a person with bipolar disorder experiences a severe stressor, is that person likely to experience an increase in symptoms? At first glance, these last two questions may appear similar, but they are not. A person with bipolar disorder could become depressed due to medication issues, social isolation, hopelessness about the disorder, or any number of other problems. As a result, negative life events per se may not be a common explanation for bipolar depression. Nonetheless, it could still be the case that when a negative life event occurs, a person with bipolar disorder could be at high risk for depression. In a psychopathology with such multifactorial etiology, it is important to distinguish two orthogonal questions: (1) Are most episodes explained by life events? and (2) Do life events predict increases in symptoms? Because there are many potential confounds in life stress studies, within-subject comparisons are important to evaluate these questions.

2. Measurement issues in studies of life events and bipolar disorder

Unfortunately, many of the measures in the life stress field can be criticized on psychometric and conceptual grounds (see Johnson & Roberts, 1995). Measurement error is not random. Bipolar symptoms are distressing, and people are highly motivated to find evidence that their episodes were triggered, and thereby will be somewhat predictable in the future. In the search for explanations, people

may be reassured if they can identify life events in the months before episode onset. This potential for systematic error mandates careful measurement. Several strategies have been developed to control for errors and biases in the identification, dating, and evaluation of life events.

In gathering life events data, a first goal is to ensure that all participants think about a full range of life events, rather than reporting just those events they construe as meaningful to their disorder. That is, assuming that people are motivated to find explanations of their disorder, a researcher must provide opportunities for people to recall events that are not salient. Beyond issues of selective presentation of events, it is important to consider that bipolar disorder changes lives. Sadly, some people with this disorder lose friends, marriages, and productive roles. Participation in fewer roles may limit the opportunities for certain kinds of stressors to occur (e.g., a person on disability has little chance of experiencing a lay-off, and a person with few friends has a smaller number of chances for major interpersonal conflicts). People may develop other types of roles or find meaning in roles such as participation in volunteer positions; these types of activities are rarely captured in standard life stress questionnaires.

Beyond the need to capture idiosyncratic experiences, specific dimensions of stress may be difficult to capture without extensive probing. For example, life events involving humiliation appear to predict depression among men (Kendler, Hettema, Butera, Gardner, & Prescott, 2003), and such events may not be probed in shorter interviews. To avoid bias, and to capture potentially idiosyncratic events, it is important to capture a very broad range of events. All interviews described in this review cover at least 57 different types of stressors (cf. Paykel, 1997). The LEDS covers more than 200 different types of life stressors (Brown & Harris, 1978).

Regardless of the number of queries in an interview, people gradually forget life events. Major life events tend to be remembered for about a year (Paykel, 1997), but a substantial proportion of minor events are forgotten quickly (Brown & Harris, 1982). Similarly, as we will discuss in more detail below, schedule-disrupting life events appear to be forgotten within 2 months (Winett, 2001). Unfortunately, some investigators asked patients to recall whether their initial episodes of bipolar disorder, which often occurred years before the interview, were triggered by negative events. Because of the likely inaccuracy of such long-term recall, I will not review such studies here.

Even in studies of a recent episode, the limits of memory are important to consider. With a median duration of depressive episodes of 9 months, life events in the year before onset will fall outside the time frame for accurate recall. Because manias tend to be much shorter than depressions (Judd et al., 2002), retrospective comparisons of life event rates before mania and depression are particularly biased. Because any differences could be artifactual, retrospective comparisons of depression and mania that used unmatched durations of recall also are not reviewed.

Even if a person recalls a life event, he or she may shift the timing of events to help explain episode onset (see Monroe & Simons, 1991). Over time, memories of life events become more biased to support the idea that life events triggered episodes (Brown & Harris, 1982). Empirical research suggests that calendars with anchors such as holidays, moves, job changes, and other major life style changes enhance accuracy, as does placing incidents in relationship to each other (Shum, 1998).

In an ideal world, researchers might use daily assessments, or even experience-sampling methods which provide daily data about stressors. Major life events, though, are relatively uncommon. Many people go an entire year without experiencing a single major life event, and few people experience more than one in a given year. Studies of daily events, then, are likely to be stymied by the low base rates of major life events. Nonetheless, these types of methods provide an excellent approach for studying reactivity to minor life events.

Given accurate identification and dating of events, there are several ways to rate the severity of a given event. Although subjective ratings are common, they are problematic, because people who are depressed may evaluate a given circumstance more negatively and people with mania may evaluate a given circumstance more positively. Another solution is to assign a standard number of points for each type of life event. A third strategy has been to consider context in evaluating event severity (Brown & Harris, 1989). That is, the end of a 3-month fling is not likely to be as painful as the end of a 10-year relationship. Similarly, pregnancy is likely to be more stressful for an unmarried teenager with little fiscal or emotional support than for a happily married woman who has planned for the event.

It is exceedingly difficult to evaluate context using a self-report measure. Self-report items such as “serious illness of a family member” may be endorsed for a broad range of stressors, from a distant aunt’s blood pressure to a spouse’s cancer. To provide a more accurate index of the objective severity of events, interviews cover context for each event. The interviewer then presents each event and its relevant contextual details to a group of raters without describing emotional reactions to the event. Discrepancies among raters are resolved by consensus.

One other potential confound deserves comment. As well-documented by Hammen (1992), symptoms of mental illness can contribute to the creation of stress. For example, negative affect can produce marital conflict, and exhaustion can interfere with work productivity. It is important to distinguish life events that are caused by poor coping and psychiatric symptoms from those that occur “out of the blue,” such as earthquakes. Many life event interviews incorporate coding for ‘independence,’ or the extent to which an event was caused by personality or psychopathology. Recent evidence suggests that such ratings can be successfully employed even within large-scale studies; in one major twin study, ‘dependent’ but not ‘independent’ life events were found to be heritable (Kendler, Karkowski, & Prescott, 1999).

Many of these procedures (extensive prompts for potential stressors, coverage of no more than 1 year, use of calendars and temporal reminders, objective ratings of severity, dictionary examples to anchor event severity ratings, consideration of life context, and evaluation of event independence) were developed to enhance the interpretability of findings. But the care involved in these types of assessments has provided strong support for life events as a predictor of many different types of psychopathology. For example, in a broad range of studies, the LEDS, one measure that includes these types of methodological innovations, has achieved substantially stronger effect sizes than self-administered measures have. Perhaps this reflects the poor inter-rater reliability, low test–retest reliability, and limited validity for self-report checklists (see Gorman, 1995 for a review). For example, in one study, only 39% of events identified by questionnaire were considered significant life stressors after further information was collected by interview (McQuaid et al., 1992). Unfortunately, most investigations of bipolar disorder have relied on self-administered measures of stressful life events, which cannot provide careful control over reporting biases and other sources of error variance.

3. Sample definition in studies of life events and bipolar disorder

For the most part, this review focuses on studies of bipolar I disorder. Some researchers, however, assessed high-risk samples to study mechanisms related to life event effects. In high-risk studies, two self-administered scales have been used to identify individuals at risk for bipolar disorder, the Hypomanic Personality Scale (HPS; Eckblad & Chapman, 1986) and the General Behavior Inventory (GBI; Depue et al., 1981). Both scales have been shown to have relatively high sensitivity and

specificity for clinical diagnoses of bipolar spectrum disorders, concurrently and in follow-up studies (Altman, 2003). I will label high-risk studies.

4. Review of life event findings in bipolar disorder

For reasons detailed above, this review covers only studies that included life stress interviews, focused on life events occurring within 1 year of the interview, employed contextual ratings to evaluate the intensity of stressors (for both negative and positive events), and analyzed events that were independent of psychopathology. Beyond these issues, it is important to note that studies have focused on differing symptom outcomes. Studies that did not distinguish mania from depression in the outcomes are covered first. Then, I turn to studies of polarity-specific effects, first those examining symptoms of depression and then those examining symptoms of mania. Within each area, three types of studies are considered separately: comparisons of life event rates for bipolar versus other groups, comparisons of rates of life events before and after episodes, and comparisons of symptoms before and after life events. Where available, studies focused on moderators of life event effects are considered. Table 1 shows methodological details of each of the studies, including the sample definition, sample size, and life event measure.

5. Studies that do not distinguish polarity of symptoms

Most studies of life events in bipolar disorder focus on the role of negative life events. In most of these studies, researchers focus strictly on events that are severe – such as death or loss of a confidant or

Table 1
Studies of independent severe negative life events in bipolar disorder

Author (year)	Sample	<i>n</i> for bipolar group	Life events measure
Alloy et al., 1999	Students with cyclothymia, dysthymia or hypomania	43	LES
Bebbington et al., 1993	Inpatients with psychotic mania	31	revised LEDS
Christensen et al., 2003	BPD patients with at least 3 hospitalizations	56	RLE
Chung et al., 1986	Hypomanic inpatients	14	LEDS
Ellicot et al., 1990	BPD patients receiving medications and remitted	61	Revised LEDS
Hunt et al., 1992	Patients with BPD	62	RLE
Johnson & Miller, 1997	Community residents with BPD	65	LEDS
Johnson et al., 2000	Community residents with BDP	149	LEDS
Johnson et al., 2004	Community residents with BPD	59	LEDS
Kennedy et al., 1983	Inpatients with mania	20	RLE
Malkoff-Schwartz et al., 2000	Manic or cycling participants compared to control participants	45	LEDS
McPherson et al., 1993	Patients with BPD	58	RLE
Pardoen et al., 1996	Patients with recovered BPD	27	RLE
Reilly-Harrington et al., 1999	Students with RDC BP spectrum disorder		LES
Sclaire & Creed, 1990	Manic inpatients	24	LEDS

BPD—bipolar disorder. RLE—interview for recent life events. LEDS—life events and difficulties schedule. LES—self-report life events survey followed by interview and ratings.

family member, major role loss, or life-threatening illnesses, because severe events have been found to be especially predictive for other psychopathologies (Brown & Harris, 1989). Many interview-based studies document a robust influence of independent, severe negative life events on the course of bipolar disorder (see Johnson & Roberts, 1995 for a review). For example, life events appear to be more common before relapse than they are before other periods in the life of people with bipolar disorder. For example, Hunt, Bruce-Jones, and Silverstone (1992) found an approximate fourfold elevation in the rates of severe life events in the month before relapse compared to other months among patients with bipolar disorder. Malkoff-Schwartz et al. (1998) found an approximate twofold increase in severe life events in the 8 weeks preceding an episode compared to a control period. One study failed to find an increase in life events in the 3 months before episodes (McPherson, Herbison, & Romans, 1993).

Beyond the cross-sectional studies, two longitudinal studies have shown robust predictive power for life events. For example, severe, independent, negative life events were found to predict a fourfold increase in risk of relapse (Ellicot, Hammen, Gitlin, Brown, & Jamison, 1990), and a threefold increase in the time until recovery (Johnson & Miller, 1997). Summing across cross-sectional and longitudinal studies, then, studies generally provide evidence for the effects of life events on the course of illness, despite one nonreplication.

Researchers also have examined variables that could buffer the effects of life events. Some studies have obtained null effects, perhaps due to low statistical power. As Table 1 shows, almost all studies of life events in bipolar disorder have included fewer than 70 people. In most studies, many people did not relapse, further limiting the participants available for certain analyses. Small sample sizes would limit power to detect interaction effects. For example, one report based on 59 participants suggested that social support did not buffer the effects of life events (Johnson, Winett, Meyer, Greenhouse, & Miller, 1999). In contrast, obsessiveness and introversion have been found to predict greater life event reactivity (Swendsen, Hammen, Heller, & Gitlin, 1995). Interpersonal events, interpersonal dependency, and the interaction of the two have been found to predict higher symptom severity scores (Hammen, Ellicott, & Gitlin, 1992) and faster relapse (Fingerhut, 2000). In keeping with the importance of interpersonal stressors, Expressed Emotion, or family criticism regarding a patient's illness, has been shown to predict poorer outcomes for patients with bipolar disorder in a series of studies (Butzlaff & Hooley, 1998). Personality traits and interpersonal stressors, then, may be important predictors.

Illness characteristics have received particular focus as potential moderators. Post and Weis (1998) theorized that life events may be likely to trigger early episodes of mood disorders, but that the course of illness may become more severe and less driven by external triggers over time. Despite the prominence of this model, two longitudinal studies with careful symptom measures failed to find evidence that episodes of bipolar disorder become more frequent over time (Coryell et al., 2003; Turvey et al., 1999). Regardless of whether episodes become more frequent over time, the most critical data for this review are whether episodes become less tied to life events over time. Two research studies with careful life event interviews provide contrasts of people with late versus early episodes, and these two studies yielded inconsistent results. Hammen and Gitlin (1997) found that number of previous episodes of illness predicted greater life event reactivity, but Hlastala et al. (2000) did not. Despite these inconsistent results, other aspects of illness history may be important. Aronson and Shukla (1987) found that subsyndromal symptoms of disorder predicted relapse after an earthquake. In early research, then, people who are already symptomatic when encountering a life event may react more strongly.

In sum, findings of most studies suggest that independent, severe negative life events predict faster relapse and slower recovery within bipolar disorder. Preliminary research suggests a few key buffers are

important to consider. Keep in mind, however, that the studies reviewed in this section did not differentiate between depression and mania.

6. Polarity-specific effects

There are several reasons to proceed on the assumption that depressive and manic episodes may be related to different types of life events. At a basic level, it is important to clarify that people with bipolar disorder differ in how much depression they experience. The diagnostic criteria for bipolar I disorder specify only a single manic or mixed episode and do not require an episode of depression (APA, 2002). Although depressive episodes are normative in clinical settings, available epidemiological studies consistently identify a subgroup characterized by unipolar mania: 25–33% of people with bipolar disorder report no lifetime history of major depression when community epidemiological samples are surveyed (cf. Karkowski & Kendler, 1997; Kessler, Rubinow, Holmes, Ableson, & Zhao, 1997). Some have suggested that these people will experience a depression eventually or at least milder symptoms of depression, but in one study, people with unipolar mania were found to remain free of major depressive episodes for more than 20 years (Solomon et al., 2003). Certainly, debate continues regarding how common unipolar mania is, but the existence of these cases points towards the need to consider that some people with bipolar disorder experience much less depression than do others.

A set of studies suggest that the predictors of mania and depression differ. Intriguingly, a recent twin study suggests that the genetic vulnerability for mania and depression, although related, is separable (McGuffin et al., 2003). It is important to distinguish depression from mania in studies of psychosocial predictors (Johnson and Kizer, 2002) and neurotransmitter correlates (Joffe, Young, & MacQueen, 1999).

Many studies demonstrate strong comparability between bipolar and unipolar depression (see Johnson & Kizer, 2002 for a review). For example, both bipolar and unipolar depressive episodes are associated with low social support, low self-esteem, and maladaptive cognitive styles. Moreover, negative cognitive styles and low social support both predict increases in depressive symptoms over time for people with bipolar disorder (Johnson & Fingerhut, 2004; Johnson et al., 1999). There is good reason to suggest that most psychosocial models of unipolar depression will be applicable to bipolar depression (Cuellar, Johnson, & Winters, 2005). The following section reviews the specific forms of life events that appear most predictive of depression within bipolar disorder.

6.1. Life events and depression

Negative life events have been one of the most robust predictors of unipolar depression (Brown & Harris, 1989). Not surprisingly, then, investigators also have examined negative life events and bipolar depression. Although researchers have considered other types of life events, no support has been obtained for schedule-disrupting life events (Malkoff-Schwartz et al., 1998, 2000) nor goal attainment life events as triggers of depression (Johnson et al., 2000; Johnson, Kizer, Ruggero, Goodnick, & Miller, 2004). The focus of this section, then, is on negative life events and depression.

6.1.1. Are negative life events as common before bipolar depression as before unipolar depression?

If life events predict bipolar depression, one would expect life events to be equally common before bipolar and unipolar depression. Two studies examined how common independent, severe negative life

events are before bipolar depression compared to unipolar depression. Each study found comparable rates of independent, severe life events for these two groups (Malkoff-Schwartz et al., 2000; Pardoen et al., 1996). Few studies have examined specific depressive symptoms. In one exception, however, Isometsa, Heikinen, Henriksson, Aro, and Lonnquist et al. (1995) found that approximately two-thirds of people who committed suicide had experienced a recent negative life event, with comparable rates of life events for unipolar and bipolar disorder. In sum, it would appear that independent, severe negative life events are as common before bipolar depression as they are before unipolar depression, and they are as common before suicide in bipolar disorder as before suicide in unipolar disorder.

6.1.2. Are life events more common before episodes of depression than they are before other life periods?

Several studies examined whether life events are more common before depression than they are during control periods for people with bipolar disorder. An important decision in such studies is how to define the control period. Only three studies used a control period that was close enough to the interview to be accurately recalled, and that did not fall in the year before depression onset (life events during that year are expected to be higher). Two of those studies found no difference in the rate of life events during the pre-episode and control period (McPherson et al., 1993; Pardoen et al., 1996). Christensen et al. (2003) found that negative life events preceded 50% of depressive episodes among women with bipolar disorder, but none of the depressive episodes experienced among men with bipolar disorder. Two of three studies, then, suggest that negative life events do not cluster before the depressive episode, and one suggests that negative life events may be common before depression for women.

Findings from the different types of designs, then, are not consistent. That is, life events are equally common before bipolar and unipolar depression. Given this, one might expect negative life events to be elevated before bipolar depression compared to other periods in the life of people with bipolar disorder. The evidence does not support this latter pattern, however.

Why the difference in results? Certainly methodological issues are worth considering, particularly in the three studies comparing rates of life events before and after episodes. One of these studies also failed to find a difference between unipolar and a healthy control group in rates of life events (Pardoen et al., 1996). Given that 12 studies with careful methodologies have documented robust links between unipolar depression and life events (Brown & Harris, 1989), this null effect for depression in both diagnostic groups could reflect methodological issues, such as low power: only one person with bipolar disorder experienced a major depressive episode during the follow-up period. Other issues may be important in the other two studies. For example, whereas studies in the unipolar field typically cover life events in the 9–12 months before episodes, these two studies only covered events in the 3 months before episode (Christensen et al., 2003; McPherson et al., 1993). All three studies relied on briefer interviews that may not capture the full range of events. In sum, studies covering a broader range of events, more time before episodes, and longer follow-up periods, are needed. Until the successful procedures from the unipolar depression field are applied, we will not know what proportion of bipolar depressive episodes are triggered by life events.

Beyond methodology, however, it could be that most bipolar depressions do not follow independent negative life events. Similar findings within more careful studies would be congruent with the idea that many bipolar depressions are triggered by other variables. Neurobiological changes, medication changes, family criticism, lack of social support, chronic stressors, and illness-related concerns could lead to depression in the absence of an independent life event.

6.1.3. Do life events predict increases in depressive symptoms?

In contrast to the mixed information about whether depressive episodes are commonly preceded by life events, there is evidence that negative life events predict increases in depressive symptoms. For example, in a longitudinal study of 149 participants with bipolar I disorder, negative life events, as measured using the LEDS, predicted increases in depressive symptoms over several months even after controlling for baseline levels of depressive symptoms (Johnson et al., 2004). It should be noted, however, that negative life events predicted only a small variance.

Given the small effect sizes, it is not surprising that findings have been inconsistent. Perhaps some, but not all, people develop depressive symptoms after a negative life event. Some researchers have begun to examine whether risk variables for unipolar depression are present among all people with bipolar disorder, or just those who experience depression. In a study of undergraduates with bipolar spectrum symptoms, Alloy, Reilly-Harrington, Fresco, Whitehouse, and Zechmeister (1999) documented negative cognitive styles only among those with a history of depressive symptoms. Hence, risk variables for depression may be more impactful among people with a history of bipolar depression than for those with unipolar mania. If this model holds, one might expect that reactivity to negative life events would be more pronounced among people who are vulnerable to depression.

Two studies suggest that the effects of life events emerge among a subgroup that one would expect to be more vulnerable to depression—people with depressogenic cognitive styles. Two studies of undergraduates with a history of hypomanic or depressive symptoms found that negative life events predicted increases in depressive symptoms only among students with a negative cognitive style (Alloy et al., 1999; Reilly-Harrington, Alloy, Fresco, & Whitehouse, 1999). Hence, certain subgroups of people, but not others, may be more likely to demonstrate depressive symptoms after negative life events. Further research is needed to examine this moderator in samples composed entirely of people diagnosed with bipolar I disorder.

6.1.4. Summary of life events and depression

There is strong evidence that psychosocial triggers are comparable for unipolar and bipolar depression. One would expect, then, that negative life events would be strongly predictive of bipolar depression. Congruent with this, rates of life events before bipolar and unipolar depressive episodes appear to be comparable. On the other hand, life events are not that common before bipolar depression, congruent with the idea that people become depressed for many different reasons. Although negative life events predicted increases in depression in the largest study (Johnson et al., 2004), other studies found such effects only within subgroups. Negative life events may be more predictive among people at higher risk for depression—women and persons with negative cognitive styles.

6.2. Life events and mania

Because mania is the defining feature of bipolar disorder, understanding predictors of mania is fundamental to understanding the disorder. Many types of life events have been studied in this regard, including negative events, schedule-disrupting events, and goal attainment events.

6.2.1. Negative life events

Intuitively, it might not seem reasonable to expect symptoms of mania, such as euphoria, elevated self-esteem, and increased productivity, to follow negative life events. It is worth considering, though,

that severe stressors have been found to promote a broad array of psychiatric and physical outcomes, including episodes of schizophrenia (Day, 1989), common colds (Cohen et al., 1998), and ulcers (Gilligan, Fung, Piper, & Tennant, 1987). Given the diversity of outcomes triggered by negative life events, it may not be so unreasonable to expect that life stress could induce mania as well.

Indeed, psychodynamic models focused on ‘the manic defense’ (Adler, 1964). In these models, mania was seen as a flight from painful feelings. These models predict that mania will occur after negative life events, as a defensive reaction. Newer cognitive behavioral formulations have proposed that people with bipolar disorder might avoid focusing on threatening information (Lyon, Startup, & Bentall, 1999).

A key feature of the manic defense model is the idea that people with bipolar disorder have high levels of defensiveness against painful thoughts or experiences. To test this model, authors have drawn from discrepancies in responses on overt measures of self-esteem compared to subtle measures with less potential for response bias (Bentall & Thompson, 1990; Lyon et al., 1999; Winters & Neale, 1985). Whereas most people receive similar self-esteem scores from overt and subtle measures, people with bipolar disorder tend to deny that they see themselves negatively yet also say they would blame themselves when things go badly (a more subtle measure of self-esteem). Such results have been interpreted as evidence that although people with bipolar disorder may actually perceive themselves negatively, they ward such thoughts off consciously. Beyond such discordancies, findings from a terror management study also provide some evidence for defensive reactions among people who are vulnerable to hypomania as defined by the HPS (Johnson, Ballister, & Joiner, 2005). Undergraduates with high HPS scores were more likely to show defensive reactions (increased endorsement of materialistic goals) after writing an essay about their own death. In sum, people with bipolar disorder may not acknowledge negative feelings about the self and may show more defensive behavior after a threat.

Could this defensive reaction to threat lead to a manic episode after a serious life event? In thinking about this question, it is important to consider differences between simply being defensive, and being so defensive that one actually begins to be in an overly active state that could lead towards mania. Bipolar disorder has not been found to be associated with happiness after minor life events. That is, people with bipolar disorder have been found to report less positive affect (PA) than healthy controls did after daily life stressors (Myin Germeys, Krabbendam, Delespaul, & Van Os, 2003), and no differences in PA after laboratory failure feedback (Ruggero, 2003). Although there is no specific evidence that bipolar disorder is related to greater happiness after threat, the manic defense model remains popular, and more research is needed on coping strategies used in response to threat.

What is the evidence that negative life events can induce mania? There are many published case reports of “funeral mania,” in which people demonstrate manic symptoms at an important funeral or death (Hollender & Goldin, 1978; Krishnan, Swartz, Larson, & Santoliquido, 1984; Morgan, Beckett, & Zolese, 2001; Rickarby, 1977; Rosenman & Tayler, 1986; Sakamoto, Horikawa, & Yamazaki, 1993; Singh, Jawed, & Wilson, 1988). Although intriguing, these reports do not provide an estimate of how common this phenomenon is. In a broader analysis of 1565 first psychiatric hospital admissions, Kessing, Agerbob, and Mortensenb (2004) found that death of a mother or sibling was more common before an admission for mania than it was in the general population, but only for one kind of death—the suicide of a family member. Given the heritability of suicide and bipolar disorder, though, people with bipolar disorder would be more likely to experience family suicide at any time in their life than would people without bipolar disorder. Such deaths may not be triggers of episodes, so much as a sad consequence of the genetic loading. For this reason, studies with more careful life event assessments and statistical contrasts are important. We turn to those now.

6.2.2. *Are negative life events common before manic episodes?*

Different comparisons have been used to address this question. Some studies focused on rates of life events before manic episodes compared to rates among people with no psychiatric disorder. Some researchers found that independent severe negative life events were more common before manic episodes than among people without a psychiatric disorder (Bebbington et al., 1993; Hunt et al., 1992; Kennedy, Thompson, Stancer, Roy, & Persad, 1983), whereas one did not (Chung, Langeluddecke, & Tennant, 1986). As noted above, these retrospective group comparisons fail to evaluate whether life events are specifically elevated before manic episodes (or just generally common in this population). A better-controlled comparison is whether independent severe negative life events are more common before mania than after mania. Six studies have analyzed the presence of at least one independent severe negative life event before manic episodes compared to after a manic episode. Each of these six studies indicates that independent severe negative life events are equally common before and after manic episodes (Christensen et al., 2003; Kennedy et al., 1983; Malkoff-Schwartz et al., 2000; McPherson et al., 1993; Pardo et al., 1996; Sclaire & Creed, 1990). In sum, more carefully conducted studies do not indicate elevated rates of independent severe negative life events before mania.

6.2.3. *Do negative life events predict increases in manic symptoms?*

To date, five longitudinal studies have examined whether independent severe negative life events predict an increase from baseline levels of manic symptoms. Each of these studies found no direct effect of negative life events as a predictor of increases in manic symptoms (Alloy et al., 1999; Johnson et al., 2000; Johnson et al., 2004; McPherson et al., 1993; Reilly-Harrington et al., 1999).

Despite the absence of direct effects, some subgroups may be vulnerable to increases in manic symptoms after negative life events. In one study of undergraduates with bipolar spectrum disorders, Reilly-Harrington et al. (1999) found that life stress predicted increases in hypomanic symptoms among those students with depressogenic cognitive styles. Similar findings emerged in a study of 43 undergraduates (Alloy et al., 1999) who met criteria for subsyndromal mood disorders (hypomania, cyclothymia, and dysthymia). These findings of a reactive subgroup provide support for the manic defense model.

In a LEDS study of individual differences, Johnson et al. (2004) found that symptoms in the month before an severe negative life event predicted increases in mania. That is, people who were already mildly hypomanic before the life event demonstrated increases in manic symptoms after a negative life event. Because the life events were independent, it is unlikely that they were merely the consequence of symptomatic behavior. Rather, it seems that these life events that unfolded without the person's influence seemed to trigger an increase in manic symptoms within this subset of people. Baseline hypomanic symptoms might explain some of the cross-study differences in the link between negative life events and manic symptoms.

There is certainly a need for replication. But, given replication, why might hypomania change the nature of reactions to negative life events? People with bipolar disorder demonstrate state-dependent deficits in the ability to detect threatening cues, such as facial expressions conveying negative affect, which emerge as they become manic (Lembke & Ketter, 2002). Awareness of negative cues, then, may be lowered by mania. Speculatively, poor comprehension of the negative implications of an event could induce people who are experiencing hypomanic symptoms to view negative events as a challenge rather than a defeat. A long line of research suggests that challenges are likely to elicit increased effort and activity for most people (Wortman & Brehm, 1975). Hypothetically, increased effort could promote

overstimulation and intensified manic symptoms. Unfortunately, no studies have directly considered how people cope with life events during manic states.

6.2.4. Summary of negative life events and mania

Despite a host of positive case studies, carefully controlled studies provide no evidence that rates of independent severe negative life events are elevated before manic episodes. Similarly, there is no evidence that independent severe negative life events directly predict an increase in manic symptoms. On the other hand, three studies suggest that severe negative life events may matter for certain subgroups of people: two studies of undergraduates suggest that people with a negative cognitive style may become more hypomanic after a severe negative life event, and one study of bipolar I participants suggests that those who are already hypomanic might become more so. Nonetheless, there is no evidence for a direct effect of severe, negative life events on increases in manic symptoms.

6.3. Schedule-disrupting life events

Theory has long suggested that sleep disruption (Wehr, Sack, & Rosenthal, 1987), as well as more general schedule disruption (Ehlers, Frank, & Kupfer, 1988) might be a mechanism through which life stressors lead to increases in symptoms. Naturalistic studies suggest that manic symptoms may follow sleep loss (Leibenluft, Albert, Rosenthal, & Wehr, 1996). Congruently, more carefully controlled experimental studies indicate that more than 10% of patients with bipolar depression develop hypomanic or manic symptoms after induced sleep deprivation (Colombo, Benedetti, Barbini, Campori, & Smeraldi, 1999). Case studies suggest that increasing sleep duration may help prevent symptoms of bipolar disorder (cf. Wehr et al., 1998).

Based on these findings, researchers developed a scale to code the extent to which life events disrupted schedules (Malkoff-Schwartz et al., 1998). Ratings for this scale focused on any event that might shift a person's schedule, including starting college or ending a relationship, rather than just those events that disrupted sleep. In two retrospective studies, people with bipolar disorder reported more schedule-disrupting life events before manic than depressive onset (Malkoff-Schwartz et al., 1998, 2000). As noted above, though, such analyses are potentially problematic, given the longer window of recall for depressive periods. When rates of life events pre-onset were compared to the rate of events among control participants, schedule-disrupting events were not more common before manic periods than they were in the general population (Malkoff-Schwartz et al., 2000). Hence, it is not clear whether correlations observed between schedule-disruption and mania are confounded by duration of recall. Longitudinal research on schedule-disrupting life events is needed.

Winett (2001) found important issues for the assessment of schedule-disrupting life events. In her study, participants were asked about events that occurred in the 6 months before the interview. Unfortunately, people reported almost no schedule-disrupting life events that occurred more than a month before the interview. That is, schedule disruptions appear to be forgotten quickly. Her results, then, suggest the need to supplement life event interviews with diary methods to enhance recall, a method frequently used by the Malkoff-Schwartz team. Sleep disruptions may be important to assess on a daily or weekly basis.

In sum, sleep disruption appears to trigger manic symptoms, as evidenced by naturalistic and experimental studies. Although two retrospective studies provide some support for schedule-disrupting life events occurring before manic episodes, analyses comparing rates of such life events to the base rate

in the general population did not confirm the effect. It will be important to use frequent assessments and longitudinal designs to examine such events.

6.4. *Goal attainment life events*

For over 20 years, theorists suggested that the genetic vulnerability to bipolar disorder might be tied to dysregulation in the behavioral activation or behavioral approach system (cf. Depue, Collins, & Luciana, 1996). This brain-based system has been hypothesized to regulate cognition, affect, and behavior in situations involving pursuit of incentives and goals. To facilitate approach behavior, this system has been hypothesized to promote increases in positive affect, energy, goal pursuit and attention towards cues of reward. For many years, evidence for this model consisted of the observation that symptoms of mania mirrored the conceptually-defined outputs of this system (Depue et al., 1996).

Drawing on this model, then, one might expect that people with bipolar disorder would demonstrate increased reactivity to reward. This idea was examined using a self-report scale, the Behavioral Activation Reward Responsiveness Scale (BAS; Carver & White, 1994). On this scale, people describe how much they tend to experience increases in positive affect, energy, and motivation when cues of incentive are present. Among undergraduates, measures of vulnerability to hypomania are correlated with the BAS Reward Responsiveness Scale (Johnson & Carver, in press; Meyer, Johnson, & Carver, 1999), as well as choosing approach-oriented responses to vignettes concerning life situations (Meyer, Beevers, & Johnson, 2004). People with bipolar I endorse high Reward Responsiveness, across manic and euthymic periods (Meyer, Johnson, & Winters, 2001). In sum, a set of studies suggest that bipolar disorder is associated with stably high reward responsiveness.

Because of their high reward responsiveness, people with bipolar disorder might respond with heightened positive affect and goal-directed behavior to environmental cues of reward and incentive. A first study of this issue examined psychophysiological reactivity to negative and positive stimuli (pictures) (Sutton & Johnson, 2002). It is well-documented that when people are viewing negative stimuli, they demonstrate a heightened startle response (as measured by electromyography of the orbicularis oculi muscle region) to a loud acoustic probe. There is also evidence that when people are viewing positive stimuli, they demonstrate an attenuated startle response (Bradley, Codispoti, Cuthbert, & Lang, 2001). This paradigm has been used to study individual differences in responses to positive and negative stimuli (Cook, 1999). Sutton and Johnson (2002) examined startle responses among undergraduates with high and low scores on the HPS. As predicted, high HPS scores were related to more attenuation when viewing positive stimuli. This finding supports the idea that hypomanic vulnerability is tied to increased reactivity to cues of incentive. That is, people with bipolar disorder might differ in the way they regulate after exposure to a reward-relevant stimulus.

If mania is tied to increased reactivity after exposure to incentives, one might expect life events involving goal attainment to predict manic symptoms. This model has been examined using the LEDS goal attainment scale, which was designed to capture both interpersonal and occupational successes (Leenstra, Ormel, & Giel, 1995). The goal attainment ratings of events are more specific than general positive events, in that personal striving and commitment towards a goal were required to code an event as high in goal attainment. Although goal attainment events vary, typical examples include acceptance into graduate school, passing an extremely difficult career hurdle, or winning recognition for a poem. In the first report, life events involving goal attainment were predictive of increases in manic symptoms, but not depressive symptoms (Johnson et al., 2000). Recently, parallel results were obtained in an extended

sample of 149 participants (Johnson et al., 2004). Again, goal attainment life events predicted increases in manic symptoms over a 3-month period. Baseline symptoms before a life event did not moderate the effects; regardless of their initial mood state, goal attainment life events predicted increases in manic symptoms. These studies suggest that goal attainment life events predict increases in manic symptoms.

7. Conceptual Integration

There is now substantial evidence that life events predict the course of disorder. Many of the studies focus on negative life events, and this research suggests a substantial role of negative life events in predicting recovery and relapse.

Less research has been done on the specific types of symptoms that are predicted by life events. Studies indicate that independent severe negative life events are as common before bipolar depression as they are before unipolar depression, and that they predict increases in depression. Many depressive episodes, though, may unfold without the trigger of a negative life event. Independent severe negative life events are not common before manic episodes and do not predict increases in mania for most people with bipolar disorder. Other types of life events, though, consistently have been found to precede mania. People report more schedule-disrupting life events in the weeks before a manic episode than they do a year before the manic episode, but longitudinal studies are needed. Goal attainment life events have been found to predict increases in manic symptoms. These studies provide support for the role of life events, and much greater specificity in understanding dimensions of stressors.

Although this field of research has provided a number of promising findings, it is worth noting some limitations. One particularly important limitation is the magnitude of effects. Many of the findings for life events are quite small. In this context, measurement tools to limit error variance are important. Nonetheless, life event effects may be minor compared to the role of biological variables in the expression of symptoms. Unfortunately, studies of genetic vulnerability and psychosocial triggers have remained separate, and no attempts have been made to differentiate Gene \times Environment interactions from additive genetic estimates (see Rutter & Silberg, 2002 for discussion of these issues). In the unipolar depression field, investigators have shown that life events may guide the expression of genetic vulnerability (Caspi et al., 2003; Kendler, Gardner, & Prescott, 2002). Given the strong genetic vulnerability to bipolar disorder, there is a need to integrate genetic and psychosocial variables.

Beyond the considerable role of genetic vulnerability, a broad range of other variables are important predictors of symptoms. Considering that bipolar symptoms are predicted by expressed emotion, self-esteem, social support, cognitive styles, sleep disruption, medication, and age of onset (Johnson & Meyer, 2004), it is not surprising that life events account for only a small portion of the variance.

It is also entirely possible that life events will be influential only for certain groups of people with bipolar disorder. A few researchers have considered moderators of life stress in bipolar disorder. As described above, interpersonal dependency, introversion, and obsessionality have been found to increase risk for relapse after a negative life event. In polarity-specific analyses, cognitive vulnerability and being female both appear important for predicting depressive symptoms after negative life events, and cognitive vulnerability and pre-event hypomanic symptoms appear important for predicting manic symptoms after life events. No one has studied whether a history of depression is associated with greater vulnerability to negative life events after depression. Further, researchers have not studied whether goal regulation or

sleep hygiene could help moderate the effects of goal attainment or schedule-disrupting life events. Despite some important gains, there are many remaining questions about moderators of life events.

Given that evidence continues to support life events as predictors of symptoms and that researchers can identify who is most vulnerable after life events, there is a need to consider mediators of the life event effects. We are at an early stage in understanding the mechanisms through which life events are translated into symptoms. Some speculative mechanisms appear worth investigating.

For negative life events, the natural assumption would be that these events precipitate negative emotions and decreases in positive emotions, and that the biological regulation of emotion is more disturbed within bipolar disorder. To date, however, laboratory studies have not found strong links between bipolar disorder and emotional reactivity to negative stimuli (Ruggero, 2003; Sutton & Johnson, 2002). In contrast, research has suggested that bipolar spectrum disorders are associated with decreased cognitive performance and prolonged cortisol reactivity after laboratory stressors (Goplerud & Depue, 1985; Ruggero, 2003). People with bipolar disorder also have been shown to have greater activation of limbic regions and de-activation of prefrontal cortex regions in the context of emotion (Kruger, Seminowicz, Goldapple, Kennedy, Mayberg, 2003). Hence, shifts in cognition and brain activity after negative life events would be important candidates for study.

Findings regarding schedule-disrupting life events fit well with evidence that sleep deprivation leads to manic symptoms in some people with bipolar disorder (Colombo et al., 1999). One theorist has suggested that sleep deprivation prevents recalibration of dopamine receptor sensitivity; such a mechanism would be congruent with models of dopamine dysregulation in bipolar disorder (Ebert & Berger, 1998). If longitudinal research confirms a role for schedule-disrupting life events, it will be important to consider such mechanisms.

How might an initial success promote an increase in manic symptoms? Several studies suggest that vulnerability to mania is associated with unrealistically high confidence after an initial success (Johnson & Ruggero, 2004; Johnson, Ruggero, & Carver, *in press*; Stern & Berrenberg, 1979). Increases in confidence are tied to setting higher goals on tasks. Intriguingly, goal engagement has been found to predict increases in manic symptoms over a several month period (Lozano & Johnson, 2001). A range of research is congruent with the idea that dysregulation in goal pursuit, perhaps related to poor control of reward pathways in the brain, is an important contributor to manic symptoms (Johnson, 2005). Like negative life events, then, cognition and brain activation may be particularly important to consider in assessing the potential mediators of life events involving goal attainment.

Each of the types of life events involved in the course of bipolar disorder, then, could potentially be mediated through different mechanisms. Most models of how events are transduced into symptoms draw on laboratory analog studies. Research is needed to assess potential mediators after major life events unfold. The increasing availability of mobile monitoring devices should facilitate on-line coding of sleep, affect, and cognition after life events, providing a rich way of studying mechanisms.

Finally, many outcomes remain unexamined. For example, more than 60% of people with bipolar disorder meet lifetime criteria for an anxiety disorder (Tamam & Ozpoyraz, 2002), and more than 70% meet lifetime criteria for substance abuse or dependence (Kessler et al., 1997). The role of life events in explaining these comorbid patterns remains unknown.

Despite the pending questions, life events offer a great deal of promise as a way to provide predictability for people with bipolar disorder. Hopefully, this review has highlighted the central importance of careful assessment of life stressors. With excellent assessment tools available, it is time for the field to move towards tests of (1) the specific types of life stressors that predict the course of disorder,

(2) the types of symptoms that are influenced by these specific types of life stressors, and (3) the mechanisms that link stressors with symptoms.

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