

## Life Events, Sleep Disturbance, and Mania: An Integrated Model

Jessica C. Levenson, University of Pittsburgh Medical Center

Robin Nusslock, Northwestern University

Ellen Frank, University of Pittsburgh Medical Center

**Bipolar disorder contributes substantially to the global burden of disease. Both sleep disturbance and life events predict symptoms of mania, although the underlying mechanisms associated with these relationships have been difficult to elucidate. In this report, we explore the relationships among life events, sleep disturbance, and mania in an effort to provide support for the hypothesis that some life events lead to a disruption of sleep that may ultimately lead to the development of mania. We present an integrated conceptual model that draws on research examining the mechanisms by which life events disrupt sleep in various populations, and we evaluate the role of these mechanisms in individuals with mania. Suggestions for future work in this area are also presented.**

**Key words:** bipolar disorder, life events, mania, sleep, social rhythms. [*Clin Psychol Sci Prac* 20: 195–210, 2013]

Bipolar disorder contributes substantially to the global burden of disease and has been ranked as the sixth leading cause of disability worldwide (Fajutrao, Locklear, Priaulx, & Heyes, 2009; Murray & Lopez, 1996). The disorder is characterized by manic, hypomanic, mixed, and major depressive episodes (American Psychiatric Association [APA], 2000). The lifetime prevalence rate of bipolar I and II disorders is esti-

mated at 2.1% in the United States (Merikangas et al., 2007). Bipolar episodes are likely to recur, and the disorder is associated with the highest rates of suicide among all psychiatric disorders (Miklowitz & Johnson, 2006).

Both sleep disturbance and life events predict symptoms of mania, although the underlying mechanisms associated with these relationships have been difficult to elucidate. Examining the role of sleep disturbance and life events may help us better understand the underlying mechanisms of bipolar disorder, especially when we consider evidence implicating these factors in the development of bipolar episodes (e.g., Altman et al., 2006; Harvey, 2008; Harvey et al., 2005; Johnson, 2005; Miklowitz & Johnson, 2009; Proudfoot, Doran, Manicavasager, & Parker, 2010). Because our understanding of *how* sleep disturbance and life events contribute to bipolar episodes is not fully developed, recent work has focused specifically on elucidating the mechanisms by which these factors are involved in the etiology of bipolar disorder (Miklowitz & Johnson, 2006; Plante & Winkelman, 2008). Studying sleep in relation to manic episodes is highly relevant, because sleep disturbance is the most common prodrome of mania (Jackson, Cavanagh, & Scott, 2003). Further study that clarifies the role of these factors in the development of mania is warranted and may contribute to the development of new treatment strategies or the improvement of existing ones that target these biological and psychosocial factors.

Sleep disturbance and life events are also predictors of onsets of bipolar depression, and considerable research has been conducted on the relationship

---

Address correspondence to Ellen Frank, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, BT 812, Pittsburgh, PA 15213. E-mail: franke@upmc.edu.

between life events and depressive episodes (e.g., Hor-esh & Iancu, 2010; Johnson, 2005; Johnson et al., 2008); however, little is known about the predictors of hypersomnia, a sleep disturbance that often characterizes bipolar depression (Kaplan & Harvey, 2008). Furthermore, the types of life events and sleep disturbance that individually predict bipolar depression onset, as well as the mechanisms underlying the effect of life events on sleep that, in turn, lead to a bipolar depressive episode may differ from those relevant to mania. It may be problematic, at this point in time and without a more complete understanding of the heterogeneity of sleep disturbance that characterizes bipolar depression, to generate a model that is appropriate to both mania and bipolar depression. Thus, we limit this report to the exploration of the relationships among sleep disturbance, life events, and mania. Still, an understanding of the mechanisms by which life events disrupt sleep in the onset of bipolar depression is central to our understanding of bipolar disorder more generally. Future work should aim to generate a mechanistic model relevant to bipolar depression, and then evaluate whether there are mechanisms that overlap between the two models.

We propose that some life events lead to disturbed sleep, which ultimately predicts the onset of mania. This hypothesis is supported by evidence presented in a conceptual model that outlines three mechanisms underlying this relationship: disruptions to circadian and social rhythms, disruptions to the behavioral activation system, and emotional hyperarousal.

#### **SLEEP AND MANIA**

Sleep disturbance is one of the diagnostic criteria for an episode of mania (APA, 2000), and decreased need for sleep is a common symptom of patients in a manic episode. Furthermore, individuals with bipolar disorder often experience disturbed sleep when euthymic (Harvey et al., 2005; Plante & Winkelman, 2008), and sleep disturbance (broadly defined) may affect likelihood of relapse (Harvey, Talbot, & Gershon, 2009). The importance of sleep in mania may be best exemplified by the use of drugs that include sedation, among other properties, as an early intervention of acute mania (Plante & Winkelman, 2008), and the emphasis on regulating sleep in circadian rhythms in treating hypo-

mania with interpersonal and social rhythm therapy (IPSRT; Frank, 2005).

According to the two-process model (Borbély, 1982), sleep is regulated by a homeostatic sleep-dependent process (Process S) and a sleep-independent circadian process (Process C). Still, factors other than homeostatic and circadian processes may affect sleep (Harvey, 2008), such as environmental stressors or sleep-altering drugs.

Sleep in mood disorders may be disturbed in a number of ways. In unipolar depression, altered REM sleep and decreased delta sleep appear to be the most common changes to sleep architecture (Hetta, Rimon, & Almqvist, 1985), while increased sleep-onset latency and decreased sleep efficiency are also common. Unipolar depression and mania share the sleep abnormality of reduced delta sleep (Hetta et al., 1985), and one study (Hudson et al., 1992) found that several polysomnography (PSG) measures differentiated inpatients with mania and unipolar depression from healthy controls, including decreased total recording period, sleep efficiency, and REM latency, as well as increased number of awakenings, percentage of stage 1 sleep, and REM density. The two patient groups were similar to each other on nearly all indices of sleep. Still, those with mania had significantly less total sleep time than those with unipolar depression, which may speak to the fact that a decreased need for sleep is considered the classic sleep disturbance characteristic of mania or it may speak to potential differences between the groups in the homeostatic and circadian mechanisms underlying sleep.

#### **Previous Studies Demonstrating the Importance of Sleep in Mania**

One recent review found that 69–99% of individuals in a manic episode report a reduced need for sleep and longer sleep-onset latency (Harvey, 2008), while another identified sleep disturbance as the most robust early symptom of mania (Jackson et al., 2003). A third report identified disturbed sleep as a symptom of the distal prodrome of bipolar disorder, with 24–82% of patients identifying disturbed sleep as one of the early symptoms in five of the six studies reviewed (Skejelstad, Malt, & Holte, 2010).

Disturbed sleep is not only a symptom of mania but may also have an effect on subsequent mood. Some

studies have found that changes in sleep duration, particularly decreased sleep, predict increased mood (Bauer et al., 2006, 2008) among inpatients with bipolar disorder whose episode was of less than two weeks' duration (Barbini, Bertelli, Colombo, & Smeraldi, 1996), and among individuals with rapid-cycling bipolar disorder (Leibenluft, Albert, Rosenthal, & Wehr, 1996). Experimental work in this area has shown the depressogenic effect of sleep and the antidepressant effect of wakefulness. For example, the addition of dark therapy (DT) to treatment as usual (TAU) was associated with a faster reduction of manic symptoms than TAU alone among patients in the first two weeks of a manic episode (Barbini et al., 2005). It is unclear whether these improvements are the result of increased sleep or increased time in the dark, suggesting the possible importance of sleep rhythms and/or behavioral deactivation (discussed below) in this effect.

The antidepressant effect of sleep deprivation may be strong enough to cause a switch into mania or hypomania (Colombo, Benedetti, Barbini, Campori, & Smeraldi, 1999) in a relatively short amount of time (Salvadore et al., 2010). One relevant hypothesis states that factors that trigger manic episodes may do so via their ability to cause sleep deprivation (Wehr, 1989; Wehr, Sack, & Rosenthal, 1987), with sleep reduction (insomnia or sleep deprivation) as the final common pathway leading to mania in some cases (Wehr et al., 1987). To support this theory, a recent review (Salvadore et al., 2010) proposed mechanisms by which sleep deprivation leads to a switch into mania. Sleep deprivation may bring about its rapid antidepressant effects by activating the locus coeruleus noradrenergic system during REM sleep periods, times when the system would typically be inactive. The release of norepinephrine at this time would result in expression of certain plasticity genes, such as brain-derived neurotrophic factor (BDNF), camp-response element binding (CREB), and tyrosine kinase receptor B (TrkB), and, consequently, a rapid antidepressant response (Salvadore et al., 2010). Some life events may promote sleep deprivation (e.g., spending the night in the emergency room with a friend who has been in a car accident), so this mechanism may be important to the genesis of mania as a product of life events. Of course, in other instances, sleep disturbance may affect mood even without a preceding life event or

may promote the occurrence of life events themselves. Later we will consider these other effects.

Overall, evidence supports the role of sleep disturbance in the onset of manic episodes. Still, the relationships among these variables are not entirely clear because of the role of homeostatic, circadian, and environmental processes that may affect sleep.

#### LIFE EVENTS AND MANIA

Research has generally supported a positive association between life events and affective episodes (Alloy et al., 2005; Brown, 1989; Brown & Harris, 1978; Johnson, 2005; Johnson & Roberts, 1995; Paykel, 2001, 2003). Stress has been operationalized by some as the level of "threat severity" (Brown, 1989; Brown & Harris, 1978) or negative consequences associated with an event. Still, recent research has suggested that some events that are not typically considered "stressful" nevertheless may be important for the development of mania (discussed below). Investigating this area requires an awareness of the lack of differentiation between episode types that exists in the literature, and the fact that psychopathology itself can lead to subsequent life events (Johnson, 2005; Johnson & McMurrich, 2006; Paykel, 2001). These are notable limitations because predictors of mood episodes may not be common to both mania and depression and, if the direction of causality is not considered, life events that are *dependent* on the current mood state may be mistaken for life events that have *caused* the mood state (Bender, Alloy, Sylvia, Urosevic, & Abramson, 2010; Hammen, 2006).

Early work in this area was largely atheoretical and focused on establishing a link between life events and bipolar episodes. Many studies in this area found a positive association between mood episodes and the presence of stressful life events (or higher levels of life stress), with regard to both the first of a mood episode (Ambelas, 1979, 1987; Joffe, MacDonald, & Kutcher, 1989; Kennedy, Thompson, Stancer, Roy, & Persad, 1983; Kessing, Agerbo, & Mortensen, 2004) or prior to a relapse or recurrence (Aronson & Shukla, 1987; Ellicott, Hammen, Gitlin, Brown, & Jamison, 1990; Hammen & Gitlin, 1997; Hunt, Bruce-Jones, & Silverstone, 1992; Pardo et al., 1996).

But some of these early studies are characterized by retrospective designs and used case reports to identify

life events and control groups that are somewhat dissimilar to the patients of interest. Moreover, some work refutes the generally positive association between life events and mood episodes (Chung, Langeluddecke, & Tennant, 1986; Cohen, Hammen, Henry, & Daley, 2004; McPherson, Herbison, & Romans, 1993; Sclare & Creed, 1990), although this may be a function of methodological differences between these studies and the others cited above. For example, the small sample size of some of these studies may have increased the difficulty of detecting a statistically significant event, even when the results trended in the expected direction. In addition, one of these studies used a very conservative definition of episode onset, which may have affected the identification of life events that occurred prior to episode onset. In the Cohen et al. study, the specific main effect of life stress on manic recurrence may have been significant, but the result was not interpretable because the omnibus model predicting 12-month manic recurrence was not significant. It is also possible that the kindling hypothesis (Post, 1992) might explain the lack of association between life event and episode onset in these cases, if these individuals had a longer duration of illness. Nevertheless, in general, the literature supports the role of stressful life events in the onset and recurrence of manic episodes. Recent work, outlined below, describes *specific* types of life events and their role in the development of mania.

#### MECHANISTIC PATHWAYS BY WHICH LIFE EVENTS DISRUPT SLEEP

As part of an integrated model (see Figure 1), we explore three theoretical models and their associated mechanistic pathways that describe an effect of life events on sleep. We hypothesize: (a) some life events involve a disruption to social rhythms, which may disturb sleep via circadian rhythm disruption; (b) life events involving reward attainment may disrupt sleep in the presence of weak regulation of the behavioral approach system; (c) life events that involve threat may disrupt sleep via emotional and physiological arousal. Some of these mechanisms have been identified in individuals with mania, but others have been described in other populations.

As mentioned above, the ability of a life event to disturb sleep, which ultimately leads to the onset or exacerbation of mood symptoms, is just one possible direction of these effects. In other cases, sleep deprivation could trigger impairments in psychological and/or interpersonal functioning, as well as itself generate life events (Partinen, 1994; Russell & Browne, 2005), especially if these events are self-generated events subsequent to (hypo) mania that involves decreased sleep. Furthermore, there may be scenarios in which sleep disturbance and/or life events are the *consequence* of manic or hypomanic symptoms rather than the cause. It is easy to imagine a situation in which an individual

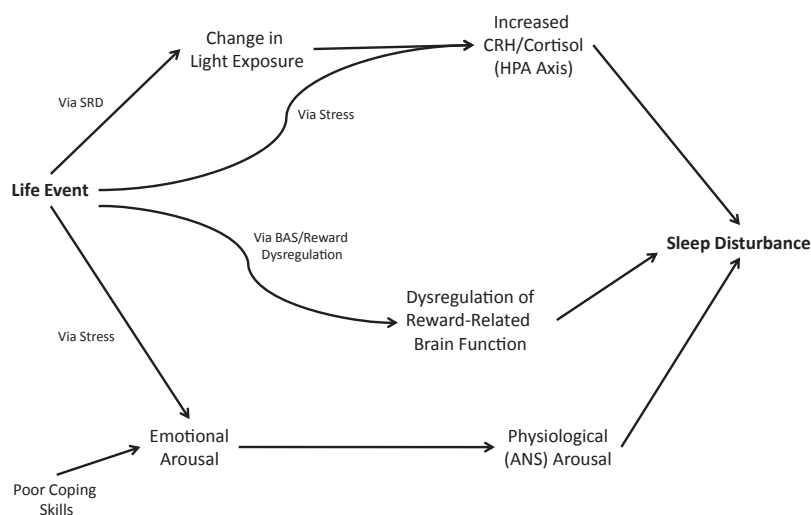


Figure 1. Integrated conceptual model: mechanisms explaining the role of life events in the onset of sleep disturbances.

in a manic state with a high level of goal seeking spends all night gambling at a casino. This, in turn, leads to sleep deprivation and the loss of large amounts of money while pursuing a big win at the slot machines. Accordingly, Urosevic et al. (2010) showed that individuals with bipolar spectrum disorders generated more reward-relevant events than healthy controls. Last, it is unclear whether disturbed sleep is a prodrome or a cause of mania (Plante & Winkelman, 2008). Paying close attention to the timing of symptom onset may help us to determine whether sleep disturbance predicts mood symptoms, whether it appears simultaneous to the onset of a mood disturbance, or whether it is the result of a mood disturbance. Each of these plausible scenarios may indicate the role of different mechanisms underlying the development of a mood episode and the causes and consequences of it. These are methodological complications to consider when investigating this area, and further work is needed to untangle cause and effect. In this work, however, we will focus on the effect of life events on sleep in the onset of mania.

#### **Sleep, Social Rhythm Disruption, and Bipolar Disorder**

Some recent work in the life events literature has focused on events that involve a disruption of social rhythms (SRD events). Losing a job, for example, may have financial implications, involving some level of threat (Brown, 1989; Brown & Harris, 1978), but it can also alter the sleep, wake, and meal times of an individual's daily schedule, that is, his or her social rhythms (Ehlers, Frank, & Kupfer, 1988; Ehlers, Kupfer, Frank, & Monk, 1993; Malkoff-Schwartz et al., 1998, 2000). Alternatively, a change in one's work shift may not cause significant stress as job security is not in jeopardy, but nonetheless can lead to a disruption of rhythms-based needing to go to and/or return from work at a different time.

Exploration of the social zeitgeber (*timegiver*) theory of affective disorders (Ehlers et al., 1988, 1993) explains how SRD events lead to mania through a disruption of sleep and circadian rhythms. This theory asserts that some life events prompt a disturbance in social zeitgebers and subsequently disrupt social rhythms. Social zeitgebers include "personal relationships, social demands, or tasks that serve to entrain biological

rhythms" (Ehlers et al., 1988, p. 948). Once social rhythms are dysregulated, biological rhythm dysregulation can result (including disrupted sleep rhythms), leading to somatic symptoms and affective episodes. Empirical support for this theory is still growing, but the role of disturbed circadian rhythms or sleep in the effect of life events on bipolar disorder has been discussed and supported by other researchers as well (Altman et al., 2006; Johnson, 2005; Russell & Browne, 2005). As mentioned above, some of these SRD events may, in fact, directly prohibit sleep, such as accompanying a friend to the emergency room at midnight or taking an overnight flight.

One study noted that SRD events occurring prior to a bipolar episode were associated with manic but not bipolar depressive episode onset (Malkoff-Schwartz et al., 1998) and that individuals with mania were more likely to report an SRD event than cycling individuals or those with unipolar depression (Malkoff-Schwartz et al., 2000). Those experiencing mania were also more likely to report an SRD event during a preonset period than during a control period (Malkoff-Schwartz et al., 1998). While these studies did not examine the effect of life events on sleep per se, one could argue that, given the definitions used for SRD events in this study, social rhythm disruption may be used as a proxy for sleep disturbance. In those with "soft" bipolar diagnoses (bipolar II disorder and/or cyclothymia), life events, particularly SRD events, prospectively predicted depressive symptoms and episodes, although their ability to predict (hypo) manic symptoms and episodes was less consistent (Sylvia, Alloy, Hafner, Gauger, & Verndon, 2009).

It may be possible to identify a couple of potential mechanisms underlying the effect of life events on sleep disruption in mania from a study of unipolar depression. This may not be altogether unexpected given the sleep architecture shared by individuals with unipolar depression and mania, and the fact that the social zeitgeber hypothesis was originally applied to unipolar depression (Ehlers et al., 1988; Healy & Williams, 1989). In a study that showed that depressed adults had more disturbed sleep following SRD events than normal controls (Haynes, McQuaid, Ancoli-Israel, & Martin, 2006), the authors suggested that the sleep/wake systems of these patients, already susceptible to



the effect of life events, may not self-correct as effectively as those of normal controls after SRD events, making dysregulation more likely. More specifically, they note that SRD events may be associated with increased exposure to light or increased levels of cortisol, two mechanisms that may affect the sleep/wake rhythm and lower the threshold for sleep disruption.

The association of SRD events with increased light exposure and/or increased cortisol levels (Haynes et al., 2006) may indicate a role of the hypothalamic-pituitary-adrenal (HPA) axis. Within this feedback loop, the hypothalamus secretes corticotropin-releasing hormone (CRH), which acts on the pituitary to stimulate the release of adrenocorticotrophic hormone (ACTH). ACTH acts on the adrenal cortex, stimulating the production and release of cortisol. It has been suggested that CRH decreases slow-wave sleep and increases wakefulness, resulting in a lowered threshold for sleep disruption (Buckley & Schatzberg, 2005; Daban, Vieta, Mackin, & Young, 2005). Thus, anything that might increase CRH production has the potential to disrupt sleep. Buckley and Schatzberg (2005) suggest that CRH production in the paraventricular nucleus (PVN) of the hypothalamus is driven by *both* the suprachiasmatic nucleus (SCN) and the stress response. This is important because SRD events have the potential to affect information pertaining to light exposure that is sent to the SCN, as well as the stress response. Photoreceptors in the eye communicate information about ambient light to the circadian clock in the SCN (Duffy & Wright, 2005), which connects directly and indirectly with the PVN of the hypothalamus (Buckley & Schatzberg, 2005), driving the release of CRH and cortisol. As even a weak light stimulus can phase shift endogenous melatonin and cortisol rhythms (Boivin & Czeisler, 1998), SRD events can disrupt sleep and circadian rhythms via the effect of increased light exposure on CRH production via the SCN. Because supersensitivity to light is thought to be a trait marker of bipolar disorder (Lewy et al., 1985), changes in light exposure that result from SRD events may have a more potent effect on sleep/wake and circadian rhythms among individuals with the disorder than would be seen in healthy individuals.

So, the HPA axis may be important to the effect of SRD events on sleep based on changes in light expo-

sure. As the HPA axis is activated during times of physical or psychological stress (Daban et al., 2005), SRD events may also predict sleep disruption based on the extent to which these events involve conventional levels of stress. Buckley and Schatzberg (2005) note that glucocorticoid receptors may be activated during stress, increasing CRH. Again, CRH decreases slow-wave sleep and increases light sleep and wakefulness. Taking these two mechanisms together, CRH can contribute to “stressed and nonstressed waking” (p. 3109). Together with the fact that HPA axis abnormalities are thought to be trait markers of bipolar disorder in general (Daban et al., 2005; Watson, Gallagher, Ritchie, Ferrier, & Young, 2004), these findings highlight the importance of increased light exposure, stress, and HPA axis hyperactivation in the development of disturbed sleep.

It has been proposed that other external factors also entrain rhythms in humans and animals, either alone or in combination with light, including temperature, nutrition, and exercise (Misteleberger & Skene, 2005; Ronnenberg & Mellow, 2007; Shibata, Tahara, & Hirao, 2010). This may be important if an SRD event involves a change in mealtimes, work schedule, or other environmental factors, in addition to light exposure. Overall, we have proposed that SRD events may have an effect on sleep. This may occur because social rhythm disruption may be a proxy for sleep disruption, so the extent of social rhythm disruption associated with an event may point to the expected sleep disturbance. Alternatively, the extent to which SRD events are associated with changes in light exposure or conventional levels of stress may also predict sleep disruption because of the effect of these factors on sleep via the mechanisms within the HPA axis.

#### **BEHAVIORAL APPROACH SYSTEM SENSITIVITY, BIPOLAR DISORDER, AND SLEEP**

Reward-striving and reward-attainment relevant life events are also important to the timing, polarity, and onset of bipolar episodes (Johnson, 2005). Research on the role of these events in bipolar episodes is predicated on the hypothesis that bipolar disorder is characterized by a hypersensitivity of the behavioral approach system (BAS), which regulates appetitive motivation and behavior to obtain rewards and/or avoid punishment

(Alloy & Abramson, 2010; Depue & Iacono, 1989; Urosevic, Abramson, Harmon-Jones, & Alloy, 2008). This model proposes that individuals with bipolar disorder are prone to experience an excessive increase in approach- or reward-related affect to reward-relevant cues, which, in the extreme, is reflected in hypo/manic symptoms (Alloy & Abramson, 2010; Depue & Iacono, 1989; Urosevic et al., 2008). Compared to relevant control groups, bipolar individuals display elevated scores on self-report measures of both BAS sensitivity and sensitivity to reward-relevant cues (Alloy & Abramson, 2010; Alloy et al., 2006, 2008; Carver & Johnson, 2009; Gruber & Johnson, 2009; Johnson & Carver, 2006; Meyer, Johnson, & Carver, 1999; Meyer, Johnson, & Winters, 2001; Salavert et al., 2007). Among bipolar spectrum individuals, elevated self-reported BAS sensitivity prospectively predicts shorter time to onset of hypo/manic episodes (Alloy et al., 2008) and a greater likelihood of converting from cyclothymia/bipolar II disorder to bipolar I disorder (Alloy et al., 2011). Individuals with both bipolar I disorder and a bipolar spectrum disorder display elevated reward/approach-related brain activity, as indexed by both electroencephalography (Harmon-Jones et al., 2008; Nusslock et al., 2012), and fMRI (Nusslock et al., 2012). Finally, and relevant to the present report, both reward-striving and reward-attainment relevant life events have been shown to trigger hypo/manic episodes (Johnson, Meyer, Winett, & Small, 2000; Johnson & Sandrow, 2000; Nusslock, Abramson, Harmon-Jones, Alloy, & Hogan, 2007).

The social zeitgeber and BAS/reward models of bipolar disorders can be integrated in a complimentary fashion given that many reward-relevant events (e.g., goal striving, goal attainment) can disrupt social rhythms. Highly reward-sensitive individuals may also be more vulnerable to social rhythm disruption in response to reward-relevant events, and greater social rhythm disruption in response to reward-relevant events predicts increases in bipolar episodes and first onset of a bipolar spectrum diagnosis (Boland, Bender, LaBelle, Abramson, & Alloy, 2012). Furthermore, individuals with bipolar disorder may generate the very reward-relevant events that disrupt social rhythms and trigger bipolar episodes. As noted above, Urosevic et al. (2010) reported that bipolar individuals generate

more reward activation (e.g., goal striving) and reward deactivation (e.g., failures) events as compared to healthy controls. The high achievement motivation (Johnson, 2005) and reward sensitivity among individuals with bipolar disorder can lead to working excessively long hours and neglecting important social routines (Nusslock et al., 2009). In extreme cases, this can involve extreme sleep loss and disruption of circadian rhythms. In line with this view, the two most common prodromes of a manic episode are increased reward-directed activity and decreased need for sleep (Lam & Wong, 1997).

There is also an important coupling between reward-processing and social/circadian rhythm variables at the biological level of analysis. Growing evidence suggests that activity in the reward system may be partly determined by timing information from the SCN, such that reward motivation is greatest when the environment is most likely to produce rewards (daytime for diurnal species; see Murray et al., 2009; Murray & Harvey, 2010; for review). Positive affect, subjective alertness, and heart rate responses to reward-related stimuli show a circadian rhythm and reach their zenith in the late afternoon, whereas negative affect does not show such daily variation (Clark, Watson, & Leeka, 1989; Goel, Van Dongen, & Dinges, 2011; Hasler, Mehl, Bootzin, & Vazire, 2008; Murray, Allen, & Trinder, 2002; Murray et al., 2009). Animal studies report circadian genes from the clock pathway influence behavioral indices of reward function (Andreatic, Chaney, & Hirsh, 1999; McClung et al., 2005) and mice carrying a mutation of the CLOCK gene exhibit manic-like behavior (e.g., hyperactivity, greater valuing of cocaine; Roybal et al., 2007). Finally, recent research has examined the relationship between reward-related brain function in humans and circadian genes (Forbes et al., 2011).

Despite the relationship between reward and social rhythm/sleep-related variables, there are many unanswered questions as to how these variables interact to generate vulnerability to manic episodes. Under certain circumstances, SRD events likely precede manic symptoms such as excessive goal-striving behaviors and approach-related affect, as proposed by the social zeitgeber perspective (Ehlers et al., 1988, 1993). Under other circumstances, excessive goal-striving-related

behaviors and reward responsivity may precipitate SRD, as proposed by the BAS hypersensitivity perspective (Alloy & Abramson, 2010). Thus, the relationship between social/sleep disruption and reward processing in vulnerability to manic episodes is likely bidirectional, with one serving as a causal factor for the other, under certain circumstances. Future research, however, is needed to test this perspective. This research should not only consider the circumstances under which SRD events precede reward-related events in the causal chain to manic episodes, and vice versa, but also the biological mechanisms by which these vulnerabilities operate to produce mania.

### **Insomnia, Mania, and Hyperarousal to Stress**

We now turn to the literature providing evidence for the role of life events in the development of insomnia *per se*. To the extent that the sleep disturbance seen in insomnia may resemble, in some ways, the sleep disturbance seen in mania (e.g., Hetta et al., 1985; Hudson et al., 1992), we may be able to generate additional hypotheses about the mechanisms underlying this effect. Moreover, in their influential work on the development of mania, Wehr et al. (1987) suggest that the insomnia that occurs as a consequence of some life events may be one sleep disruption that results in reduced sleep, which ultimately leads to mania. Thus, any mechanisms by which life events lead to insomnia may be relevant to insomnia that mediates the effect of some life events on mania.

Past work has shown that up to 78% of individuals with insomnia reported at least one precipitating event preceding insomnia onset (Bastien, Vallieres, & Morin, 2004). Individuals suffering from chronic insomnia reported more stress in the year before insomnia onset than a different year in their lives and as compared to good sleepers (Healey et al., 1981), with negative events involving family and social situations (Bernert, Merrill, Braithwaite, Van Orden, & Joiner, 2007) and factors related to health, family, and work or school stress (Bastien et al., 2004) being some of the most salient predictors of the disorder.

Arousal has been suggested as the main mechanism mediating the effect of life events on sleep in insomnia. Some empirical evidence suggests cognitive and physiological arousal differences between individuals with

insomnia and healthy controls (Drake, Roehrs, & Roth, 2003), while others report that emotion circuits can affect both homeostatic and circadian sleep drives (Harvey, Murray, Chandler, & Soehner, 2011). This is important because stress may lead to sleep trouble after internalization of stressful life events, leading to emotional and physiological activation (Healey et al., 1981). Morin, Rodrigue, and Ivers (2003) similarly suggested that an individual's level of bedtime arousal and coping skills mediated the effect of perceived stress on insomnia. They explain that poor sleepers rely on maladaptive emotion-oriented coping strategies when faced with life stress, maintaining hyperarousal at bedtime.

To explain this elevated arousal response, Drake et al. (2003) point to an overactivation of the stress response system, which may implicate both the HPA axis and the autonomic nervous system (ANS). Hyperactivation of the HPA axis here is likely to be similar to the mechanism described earlier in this report, in which life events and stress lead to hyperactivation of the HPA axis, perhaps via increased cortisol release, thereby disrupting sleep. But ANS hyperarousal is a new mechanism not yet discussed here. ANS hyperarousal can be observed by alterations to various physical measures (e.g., heart rate) and elevated scores on the multiple sleep latency test (Drake et al., 2003; Harvey, 2002). Harvey (2002) notes that individuals with insomnia demonstrate arousal of the ANS at night *and* during the day, perhaps resulting from sympathetic nervous system activation occurring when the individual is in an anxious state. A cognitive model of insomnia maintenance is proposed such that negative cognitions pertaining to getting adequate sleep lead to excessive worry and rumination, triggering autonomic arousal and emotional distress, and increased attention to sleep-related threat cues (Harvey, 2002). This cycle of worry and monitoring may perpetuate itself, ultimately resulting in a true sleep deficit.

Both Harvey's model and Healy's theory may be applicable to individuals with mania, as those with insomnia *and* bipolar disorder may engage in some type of emotion-oriented coping strategies, and they hold dysfunctional attitudes about sleep. Two recent studies (Gruber, Eidelman, & Harvey, 2008; Harvey et al., 2005) demonstrated that these patient groups did not differ on measures of sleep, rumination, worry, or



dysfunctional attitudes about sleep, but they did differ from a group of healthy controls on these measures. Although the findings pertaining to rumination and worry did not remain significant after controlling for symptoms of depression and anxiety, the authors suggest that the shared transdiagnostic processes common to both disorders may reflect shared comorbid anxiety and depressive symptoms (Gruber et al., 2008). The authors note that dysfunctional beliefs about sleep may be important in maintaining insomnia in individuals with bipolar disorder and that the individuals with bipolar disorder may have anxiety and fear about sleep, as do individuals with primary insomnia.

Extending these findings, we could hypothesize that the stress and anxiety associated with a stressful life event *itself* can produce hyperarousal, worry, and disturbed sleep in these patients. Like those with insomnia, patients with bipolar disorder may have the experience of internalized emotions, leading to physiological arousal, even if the reaction pertains to a stressful life event, rather than inadequate sleep. When combined with poor coping strategies, sleep disturbance may be even more likely to occur, which may in turn predict elevated mood. This is reminiscent of Haynes and colleagues' (2006) suggestion that patients with unipolar depression have sleep/wake systems that are less likely to self-correct after SRD, making dysregulation more likely, and of the evidence for increased mood that results from decreased sleep (e.g., Barbini et al., 1996; Bauer et al., 2006, 2008). Hyperarousal may be a normal reaction to a stressful event, but those who later develop insomnia or mania may be less capable of reversing this reaction than healthy individuals, which may lead to the development of more symptoms of mania.

When considering these mechanisms, it is also important to note the heterogeneity among individuals with mania. Some may actually desire to sleep but cannot, while others are content in their sleeplessness while engaging in activating or rewarding endeavors. We may not be able to determine whether the arousal mechanism mentioned here applies to both of these groups, given the limited data available. Some individuals early in a manic episode may desire to sleep but may not possess the skills needed to lower their arousal at bedtime, similar to some individuals with insomnia.

A second possibility is that euthymic individuals with bipolar disorder may experience decreased sleep as a result of hyperarousal following a stressful life event, and the change in sleep duration itself may lead to increased mood. It may be these individuals who experience a stressful life event that results in insomnia, ultimately leading to the onset of mania, as described by Wehr et al. (1987). Other individuals may know the appropriate strategies for facilitating sleep but still find themselves awake, or they may desire to continue engagement in activities that maintain elevated energy levels and prohibit sleep. These individuals may be further into a manic episode and their sleep disturbance may be better characterized as decreased need for sleep rather than difficulty initiating sleep.

## DISCUSSION

This review has highlighted several lines of evidence suggesting that both sleep disturbance and life events predict manic symptoms and episodes. Sleep plays a key role in the development of mania, based on both homeostatic and circadian processes. In addition, the association between various types of life events and mania is generally positive. Furthermore, life events may contribute to the development of disturbed sleep in their own right. Figure 1 shows the four mechanisms underlying this effect that have been proposed based on the empirical and theoretical work reviewed here. Events involving social rhythm disruption, or those that prohibit sleep directly, may lead to sleep and circadian rhythm disruption via a change in the amount of light exposure. Increased light exposure that accompanies a change in social rhythms may increase CRH/cortisol release, thereby disrupting sleep. Life events involving threat or stress may also increase cortisol release directly, subsequently disrupting sleep via HPA axis dysregulation. Third, reward-striving and reward-attainment relevant life events have been shown to trigger hypo/manic episodes, and there is an important coupling between reward and sleep-related variables. Future research is needed to establish under which circumstances reward-related events precipitate abnormalities in social/sleep-related variables, and vice versa, as well as the biological mechanisms through which reward and sleep-related processes interact to generate manic episodes. Last, some individuals internalize the emotions

that accompany a stressful life event, leading to physiological arousal and sleep disruption, particularly when this arousal is coupled with a lack of the coping skills needed to counteract hyperactivation. We have hypothesized that anxiety about the stressful event *itself*, rather than that pertaining to sleeplessness, may be sufficient to disrupt sleep, which is likely given the similar worry and rumination seen in those with mania and insomnia.

It is also important to consider the subpopulations and clinical presentations of bipolar disorder for which this model may be most pertinent. The objective of this model is to outline the methods by which life events disturb sleep, leading to the development of manic symptoms and/or episodes among individuals with bipolar disorder. In theory, such a model may be appropriate for any individuals who develop either threshold or subthreshold symptoms of hypo/mania. This is because we are *not* postulating that the mechanisms underlying the association of sleep disturbance and the development of hypo/manic symptoms are the same among various types of mania; rather, that the mechanisms by which *life events* disturb sleep may be common among these patient groups. The literature cited here has included studies of clinical samples with bipolar I disorder and bipolar II disorder, undergraduates with a bipolar spectrum diagnosis, as well as individuals with rapid-cycling bipolar disorder. The relative dearth of studies examining the effects of various types of life events on sleep among any one subtype of individuals with bipolar disorder makes it difficult to say definitively whether this model is more relevant for one group over another.

This calls our attention to the consideration of several limitations. The literature should more formally differentiate types of mania (sub- or full-threshold) and clinical populations when examining this area. To accomplish this, future work should ensure sufficient power to be able to study individuals with bipolar I disorder separately from bipolar II disorder, and subthreshold bipolar conditions, differentiating manic, hypomanic, and mixed episodes. This will allow us to examine the effect of life events and sleep disturbance on mood among a variety of patient groups, in an effort to accrue additional evidence for the suitability of this mechanistic model for various populations and clinical presentations. Second, the literature should

more formally differentiate life event types. Several excellent tools exist to identify the nature of an event (e.g., Brown, 1989; Brown & Harris, 1978; Frank, Anderson, Malkoff-Schwartz, & Monk, 1995), which is critically important to understanding the effects of the event. Moreover, the role of various classes of medications in these models should be explored. For example, we may expect individuals taking mood stabilizers that have an effect on the circadian system (such as lithium) may be less vulnerable to the impact of SRD events on sleep.

Last, further exploration is required regarding the extent to which mechanisms that explain the effect of life events on sleep among individuals with unipolar depression are applicable to those with mania. Part of the complication arises from the growing interest in a spectrum model of mood disorders that decreases attention to the distinction *between* unipolar and bipolar disorders and focuses instead on the presence and importance of symptoms of hypomania in those with well-established unipolar diagnoses (e.g., Cassano et al., 2002, 2004). Evidence for the spectrum approach challenges the distinction we have made here between unipolar and bipolar depression and begins to call into question the idea that *different* sleep mechanisms underlie the onset of these episodes. On the other hand, the spectrum approach does not claim that all individuals with depression experience symptoms of hypomania. It may be that the mechanisms underlying the effect of sleep on mood for individuals with few to no symptoms of hypomania may be the most applicable for individuals with mania. Future work should continue to explore the subgroups of individuals who experience depressive episodes and examine whether the sleep disturbance and the effect of sleep on mood differ among these groups. We should avoid generalizing the application of these mechanisms too broadly until this time.

Among the clinical implications, treatments for bipolar disorder should emphasize tempering the effects of life events, and patients should focus on anticipating events that can disrupt social and/or circadian rhythms, those that involve reward striving and/or reward attainment, and stressful events that have the potential to lead to hyperarousal. Clinicians can teach patients to prepare for these events and to regulate social rhythms, behavioral approach, and emotional and

physical arousal. Learning skills to counteract the effects of these events is a high priority. Moreover, cognitive strategies to reduce worry about inadequate sleep and the stress associated with an event would be useful.

There is strong support for some aspects of the integrated model but limited support for other parts. Future work should test whether SRD events are associated with increased exposure to light, and whether stressful events associated with increased levels of cortisol are subsequently associated with disturbed sleep. It would also be of interest to examine whether, and to what extent, other external factors (i.e., mealtimes) that are affected by SRD events have a disruptive effect on sleep. Third, future studies should test whether reward-striving or reward-attainment events do affect dopamine release, subsequently affecting sleep. Animal models may be useful here in their ability to include reward-related paradigms and to deliver dopamine agonists or antagonists. Future work should test the hypothesis that life events lead to emotional and physiological arousal, perhaps in the presence of poor coping skills, ultimately disturbing sleep. Last, some events may even carry the potential to affect the multiple pathways we have described. Subsequent studies are needed to determine the effect of a single event that is characterized by multiple relevant parameters (threat/stress, SRD, reward attainment). Findings from all of these studies would elucidate the impact of life events on sleep disturbance, as well as support the use of specific treatment strategies for mania.

#### CONCLUSIONS

The studies reviewed here suggest that both sleep disturbance and life events are related to manic episodes and that these processes may interact in predicting manic episodes. An integrated conceptual model suggests that SRD events may disturb sleep via changes in exposure to light and/or changes in cortisol levels, both of which implicate the HPA axis. Reward-striving and reward-attainment events may affect sleep in the presence of a weak BAS, and there is an important coupling between reward and sleep-related variables. Last, stressful life events may influence HPA axis functioning or ANS hyperarousal, both of which can affect sleep. Future work should continue to test the relationships outlined in the conceptual models.

#### REFERENCES

- Alloy, L. B., & Abramson, L. Y. (2010). The role of the behavioral approach system (BAS) in bipolar spectrum disorders. *Current Directions in Psychological Science*, *19*(3), 189–194. doi:10.1177/0963721410370292
- Alloy, L. B., Abramson, L. Y., Urosevic, S., Walshaw, P. D., Nusslock, R., & Neeren, A. M. (2005). The psychosocial context of bipolar disorder: Environmental, cognitive, and developmental risk factors. *Clinical Psychology Review*, *25*, 1043–1075. doi:10.1016/j.cpr.2005.06.006
- Alloy, L. B., Abramson, L. Y., Walshaw, P. D., Cogswell, A., Grandin, L. D., Hughes, M. E., ... Hogan, M. E. (2008). Behavioral approach system and behavioral inhibition system sensitivities and bipolar spectrum disorders: Prospective prediction of bipolar mood episodes. *Bipolar Disorders*, *10*(2), 310–322. doi:10.1111/j.1399-5618.2007.00547.x
- Alloy, L. B., Abramson, L. Y., Walshaw, P. D., Cogswell, A., Smith, J. M., Neeren, A. M., ... Nusslock, R. (2006). Behavioral approach system (BAS) sensitivity and bipolar spectrum disorders: A retrospective and concurrent behavioral high-risk design. *Motivation and Emotion*, *30*(3), 143–155. doi:10.1007/s11031-006-9003-3
- Alloy, L. B., Urosevic, S., Abramson, L. Y., Jager-Hyman, S., Nusslock, R., Whitehouse, W. G., & Hogan, M. E. (2011). Progression along the bipolar spectrum: A longitudinal study of predictors of conversion from bipolar spectrum conditions to bipolar I and II disorders. *Journal of Abnormal Psychology*, *121*(1), 16–27. doi:10.1037/a0023973
- Altman, S., Haeri, S., Cohen, L. J., Ten, A., Barron, E., Galynker, I. I., & Duhamel, K. N. (2006). Predictors of relapse in bipolar disorder: A review. *Journal of Psychiatric Practice*, *12*(5), 269–282.
- Ambelas, A. (1979). Psychologically stressful events in the precipitation of manic episodes. *British Journal of Psychiatry*, *135*, 15–21. doi:10.1192/bjp.135.1.15
- Ambelas, A. (1987). Life events and mania. *British Journal of Psychiatry*, *150*, 235–240. doi:10.1192/bjp.150.2.235
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders*, (4th ed., text rev.) Washington, DC: Author.
- Andretic, R., Chaney, S., & Hirsh, J. (1999). Requirement of circadian genes for cocaine sensitization in *Drosophila*. *Science*, *285*, 1066–1068. doi:10.1126/science.285.5430.1066
- Aronson, T. A., & Shukla, S. (1987). Life events and relapse in bipolar disorder: The impact of a catastrophic event. *Acta Psychiatrica Scandinavica*, *75*, 571–576. doi:10.1111/j.1600-0447.1987.tb02837.x

- Barbini, B., Benedetti, F., Colombo, C., Dotoli, D., Bernasconi, A., Ciagala-Fulgosi, M., ... Smeraldi, E. (2005). Dark therapy for mania: A pilot study. *Bipolar Disorders*, 7, 98–101. doi:10.1111/j.1399-5618.2004.00166.x
- Barbini, B., Bertelli, S., Colombo, C., & Smeraldi, E. (1996). Sleep loss, a possible factor in augmenting manic episode. *Psychiatry Research*, 65, 121–125. doi:10.1016/S0165-1781(96)02909-5
- Bastien, C. H., Vallieres, A., & Morin, C. M. (2004). Precipitating factors of insomnia. *Behavioral Sleep Medicine*, 2(1), 50–62. doi:10.1207/s15402010bsm0201\_5
- Bauer, M., Glenn, T., Whybrow, P. C., Grof, P., Rasgon, N., Alda, M., ... Adli, M. (2008). Changes in self-reported sleep duration predict mood changes in bipolar disorder. *Psychological Medicine*, 38, 1069–1072. doi:10.1017/S0033291708003280
- Bauer, M., Grof, P., Rasgon, N., Baschor, T., Glenn, T., & Whybrow, P. C. (2006). Temporal relation between sleep and mood in patients with bipolar disorder. *Bipolar Disorders*, 8, 160–167. doi:10.1111/j.1399-5618.2006.00294.x
- Bender, R. E., Alloy, L. B., Sylvia, L. G., Urosevic, S., & Abramson, L. Y. (2010). Generation of life events in bipolar spectrum disorders: A re-examination and extension of the stress generation theory. *Journal of Clinical Psychology*, 66(9), 907–926. doi:10.1002/jclp.20705
- Bernert, R. A., Merrill, K. A., Braithwaite, S. R., Van Orden, K. A., & Joiner, T. E., Jr. (2007). Family life stress and insomnia symptoms in a prospective evaluation of young adults. *Journal of Family Psychology*, 21(1), 58–66. doi:10.1037/0893-3200.21.1.58
- Boivin, D., & Czeisler, C. (1998). Resetting of circadian melatonin and cortisol rhythms in humans by ordinary room light. *Neuroreport*, 9(5), 779–782.
- Boland, E. M., Bender, R. E., LaBelle, D. R., Abramson, L. Y., & Alloy, L. B. (2012). *Event-specific social rhythm disruption from BAS-relevant life events predicts depressive and hypomanic symptoms and episodes in a biobehavioral high risk sample*. Manuscript submitted for publication.
- Borbély, A. A. (1982). A two-process model of sleep regulation. *Human Neurobiology*, 1, 195–204.
- Brown, G. W. (1989). Life events and measurement. In G. W. Brown & T. Harris (Eds.), *Life events and illness* (pp. 3–45). New York: Guilford Press.
- Brown, G. W., & Harris, T. (1978). *Social origins of depression: A study of psychiatric disorder in women*. New York: Free Press.
- Buckley, T. M., & Schatzberg, A. F. (2005). On the interactions of the hypothalamic-pituitary-adrenal (HPA) axis and sleep: Normal HPA axis activity and circadian rhythm, exemplary sleep disorder. *Journal of Clinical Endocrinology & Metabolism*, 90(5), 3106–3114. doi:10.1210/jc.2004-1056
- Carver, C. S., & Johnson, S. L. (2009). Tendencies toward mania and tendencies toward depression have distinct motivational, affective, and cognitive correlates. *Cognitive Therapy and Research*, 33(6), 552–569. doi:10.1007/s10608-008-9213-y
- Cassano, G. B., Frank, E., Miniati, M., Rucci, P., Fagiolini, A., Pini, S., ... Maser, J. D. (2002). Conceptual underpinnings and empirical support for the mood spectrum. *Psychiatric Clinics of North America*, 25(4), 699–712. doi:10.1016/S0193-953X(02)00025-4
- Cassano, G. B., Rucci, P., Frank, E., Fagiolini, A., Dell'Osso, L., Shear, M. K., & Kupfer, D. J. (2004). The mood spectrum in unipolar and bipolar disorder: Arguments for a unitary approach. *American Journal of Psychiatry*, 161(7), 1264–1269. doi:10.1176/appi.ajp.161.7.1264
- Chung, R. K., Langeluddecke, P., & Tennant, C. (1986). Threatening life events in the onset of schizophrenia, schizophreniform psychosis and hypomania. *British Journal of Psychiatry*, 148, 680–685. doi:10.1192/bjp.148.6.680
- Clark, L. A., Watson, D., & Leeka, J. (1989). Diurnal variation in the positive effects. *Motivation and Emotion*, 13, 205–234. doi:10.1007/BF00995536
- Cohen, A. N., Hammen, C., Henry, R. M., & Daley, S. E. (2004). Effects of stress and social support on recurrence in bipolar disorder. *Journal of Affective Disorders*, 82, 143–147. doi:10.1016/j.jad.2003.10.008
- Colombo, C., Benedetti, F., Barbini, B., Campori, E., & Smeraldi, E. (1999). Rate of switch from depression into mania after therapeutic sleep deprivation in bipolar depression. *Psychiatry Research*, 86, 267–270. doi:10.1016/S0165-1781(99)00036-0
- Daban, C., Vieta, E., Mackin, P., & Young, A. H. (2005). Hypothalamic-pituitary-adrenal axis and bipolar disorder. *Psychiatric Clinics of North America*, 28, 469–480. doi:10.1016/j.psc.2005.01.005
- Depue, R. A., & Iacono, W. G. (1989). Neurobehavioral aspects of affective disorders. *Annual Review of Psychology*, 40, 457–492. doi:10.1146/annurev.ps.40.020189.002325
- Drake, C. L., Roehrs, T., & Roth, T. (2003). Insomnia causes, consequences, and therapeutics: An overview. *Depression and Anxiety*, 18, 163–176. doi:10.1002/da.10151
- Duffy, J. F., & Wright, K. P., Jr. (2005). Entrainment of the human circadian system by light. *Journal of Biological Rhythms*, 20(4), 326–338. doi:10.1177/0748730405277983

- Ehlers, C. L., Frank, E., & Kupfer, D. J. (1988). Social zeitgebers and biological rhythms. A unified approach to understanding the etiology of depression. *Archives of General Psychiatry*, *45*(10), 948–952. doi:10.1001/archpsyc.1988.01800340076012
- Ehlers, C. L., Kupfer, D. J., Frank, E., & Monk, T. H. (1993). Biological rhythms and depression: The role of zeitgebers and zeitstörers. *Depression*, *1*, 285–293. doi:10.1016/S0006-3223(96)00241-7
- Ellicott, A., Hammen, C., Gitlin, M., Brown, G. W., & Jamison, K. (1990). Life events and the course of bipolar disorder. *American Journal of Psychiatry*, *147*, 1194–1198.
- Fajutrao, L., Locklear, J., Priaulx, J., & Heyes, A. (2009). A systematic review of the evidence of the burden of bipolar disorder in Europe. *Clinical Practice and Epidemiology in Mental Health*, *5*(3). doi:10.1186/1745-0179-5-3
- Forbes, E. E., Dahl, R. E., Almeida, J. R. C., Ferrell, R. E., Nimgaonkar, V. L., Mansour, H., ... Phillips, M. L. (2011). PER2 rs2304672 polymorphism moderates circadian-relevant reward circuitry activity in adolescents. *Biological Psychiatry*, *71*(5), 451–457. doi:10.1016/j.biopsych.2011.10.012
- Frank, E. (2005). *Treating bipolar disorder: A clinician's guide to interpersonal and social rhythm therapy*. New York: Guilford Press.
- Frank, E., Anderson, B., Malkoff-Schwartz, S., & Monk, K. (1995). *LEDS and social rhythm disruption rating manual*. Unpublished manuscript, University of Pittsburgh, Pittsburgh, PA.
- Goel, N., Van Dongen, H. P. A., & Dinges, D. F. (2011). Circadian rhythms in sleepiness, alertness, and performance. In M. H. Kryger, T. Roth, & W. C. Dement (Eds.), *Principles and practice of sleep medicine* (5th ed., pp. 445–455). Philadelphia, PA: Elsevier.
- Gruber, J., Eidelman, P., & Harvey, A. G. (2008). Transdiagnostic emotion regulation processes in bipolar disorder and insomnia. *Behaviour Research and Therapy*, *46*, 1096–1100. doi:10.1016/j.brat.2008.05.004
- Gruber, J., & Johnson, S. L. (2009). Positive emotional traits and ambitious goals among people at risk for mania: The need for specificity. *International Journal of Cognitive Therapy*, *2*(2), 176–187. doi:10.1521/ijct.2009.2.2.176
- Hammen, C. (2006). Stress generation in depression: Reflections on origins, research, and future directions. *Journal of Clinical Psychology*, *62*(9), 1065–1082. doi:10.1002/jclp.20293
- Hammen, C., & Gitlin, M. (1997). Stress reactivity in bipolar patients and its relation to prior history of disorder. *American Journal of Psychiatry*, *154*(6), 856–857.
- Harmon-Jones, E., Abramson, L. Y., Nusslock, R., Sigelman, J. D., Urosevic, S., Turonie, L. D., ... Fearn, M. (2008). Effect of bipolar disorder on left frontal cortical responses to goals differing in valence and task difficulty. *Biological Psychiatry*, *63*(7), 693–698. doi:10.1016/j.biopsych.2007.08.004
- Harvey, A. G. (2002). A cognitive model of insomnia. *Behavior Research Therapy*, *40*, 869–893. doi:10.1016/S0005-7967(01)00061-4
- Harvey, A. G. (2008). Sleep and circadian rhythms in bipolar disorder: Seeking synchrony, harmony, and regulation. *American Journal of Psychiatry*, *165*, 820–829. doi:10.1176/appi.ajp.2008.08010098
- Harvey, A. G., Murray, G., Chandler, R. A., & Soehner, A. (2011). Sleep disturbance as transdiagnostic: Consideration of neurobiological mechanisms. *Clinical Psychology Review*, *31*(2), 225–235. doi:10.1016/j.cpr.2010.04.003
- Harvey, A. G., Schmidt, D. A., Scarna, A., Neitzert Semler, C., & Goodwin, G. M. (2005). Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. *American Journal of Psychiatry*, *162*, 50–57. doi:10.1176/appi.ajp.162.1.50
- Harvey, A. G., Talbot, L. S., & Gershon, A. (2009). Sleep disturbance in bipolar disorder: Across the lifespan. *Clinical Psychology: Science and Practice*, *16*(2), 256–277. doi:10.1111/j.1468-2850.2009.01164.x
- Hasler, B. P., Mehl, M. R., Bootzin, R. R., & Vazire, S. (2008). Preliminary evidence of diurnal rhythms in everyday behaviors associated with positive affect. *Journal of Research in Personality*, *42*, 1537–1546. doi:10.1016/j.jrp.2008.07.012
- Haynes, P. L., McQuaid, J. R., Ancoli-Israel, S., & Martin, J. L. (2006). Disrupting life events and the sleep-wake cycle in depression. *Psychological Medicine*, *36*, 1363–1373. doi:10.1017/S0033291706008208
- Healey, E. S., Kales, A., Monroe, L. J., Bixler, E. O., Chamberlin, K., & Soldatos, C. R. (1981). Onset of insomnia: Role of life-stress events. *Psychosomatic Medicine*, *43*(5), 439–451.
- Healy, D., & Williams, J. M. G. (1989). Moods, misattributions, and mania: An interaction of biological and psychological factors in the pathogenesis of mania. *Psychiatric Developments*, *1*, 49–70.
- Hetta, J., Rimon, R., & Almqvist, M. (1985). Mood alterations and sleep. *Annals of Clinical Research*, *17*, 252–256.
- Horesh, N., & Iancu, I. (2010). A comparison of life events in patients with unipolar disorder or bipolar disorder and



- controls. *Comprehensive Psychiatry*, 51, 157–164. doi:10.1016/j.comppsy.2009.05.005
- Hudson, J. I., Lipinski, J. F., Keck, P. E., Jr., Aizley, H. G., Lukas, S. E., Rothschild, A. J., ... Kupfer, D. J. (1992). Polysomnographic characteristics of young manic patients: Comparison with unipolar depressed patients and normal control subjects. *Archives of General Psychiatry*, 49(5), 378–383. doi:10.1001/archpsyc.1992.01820050042006
- Hunt, N., Bruce-Jones, W., & Silverstone, T. (1992). Life events and relapse in bipolar affective disorder. *Journal of Affective Disorders*, 25, 13–20. doi:10.1016/0165-0327(92)90088
- Jackson, A., Cavanagh, J., & Scott, J. (2003). A systematic review of manic and depressive prodromes. *Journal of Affective Disorders*, 74, 209–217. doi:10.1016/S0165-0327(02)00266-5
- Joffe, R. T., MacDonald, C., & Kutcher, S. P. (1989). Life events and mania: A case-controlled study. *Psychiatry Research*, 30, 213–216.
- Johnson, S. L. (2005). Life events in bipolar disorder: Towards more specific models. *Clinical Psychology Review*, 25(8), 1008–1027. doi:10.1016/j.cpr.2005.06.004
- Johnson, S. L., & Carver, C. S. (2006). Extreme goal setting and vulnerability to mania among undiagnosed young adults. *Cognitive Therapy and Research*, 30(3), 377–395. doi:10.1007/s10608-006-9044-7
- Johnson, S. L., Cueller, A. K., Ruggero, C., Winett-Perlman, C., Goodnick, P., White, R., & Miller, I. (2008). Life events as predictors of mania and depression in bipolar I disorder. *Journal of Abnormal Psychology*, 117(2), 268–277. doi:10.1037/0021-843X.117.2.268
- Johnson, S. L., & McMurrich, S. (2006). Life events and juvenile bipolar disorder: Conceptual issues and early findings. *Development and Psychopathology*, 18, 1169–1179. doi:10.1017/S0954569406060561
- Johnson, S. L., Meyer, B., Winett, C., & Small, J. (2000). Social support and self-esteem predict changes in bipolar depression but not mania. *Journal of Affective Disorders*, 58(1), 79–86. doi:10.1016/S0165-0327(99)00133-0
- Johnson, S. L., & Roberts, J. E. (1995). Life events and bipolar disorder: Implications from biological theories. *Psychological Bulletin*, 117(3), 434–449. doi:10.1073//0033-2909.117.3.434
- Johnson, S. L., Sandrow, D., Meyer, B., Winters, R., Miller, I., Solomon, D., & Keitner, G. (2000b). Increases in manic symptoms after life events involving goal attainment. *Journal of Abnormal Psychology*, 109(4), 721–727. doi:10.1037//0021-843X.109.4.721
- Kaplan, K. A., & Harvey, A. G. (2008). Hypersomnia across mood disorders: A review and synthesis. *Sleep Medicine Reviews*, 13(4), 275–285. doi:10.1016/j.smrv.2008.1009.1001.
- Kennedy, S., Thompson, R., Stancer, H. C., Roy, A., & Persad, E. (1983). Life events precipitating mania. *British Journal of Psychiatry*, 142, 398–403. doi:10.1192/bjp.142.4.398
- Kessing, L. V., Agerbo, E., & Mortensen, P. B. (2004). Major stressful life events and other risk factors for first admission with mania. *Bipolar Disorders*, 6, 122–129. doi:10.1111/j.1399-5618.2004.00102.x
- Lam, D., & Wong, G. (1997). Prodromes, coping strategies, insight and social functioning in bipolar affective disorders. *Psychological Medicine*, 27(5), 1091–1100. doi:10.1017/S0033291797005540
- Leibenluft, E., Albert, P. S., Rosenthal, N. E., & Wehr, T. A. (1996). Relationship between sleep and mood in patients with rapid-cycling bipolar disorder. *Psychiatry Research*, 63, 161–168. doi:10.1016/0165-1781(96)02854-5
- Lewy, A., Nurnburger, J. I. Jr., Wehr, T. A., Pack, D., Becker, L. E., Powell, R. L., et al. (1985). Supersensitivity to light: Possible trait marker for manic-depressive illness. *American Journal of Psychiatry*, 142(6), 725–727.
- Malkoff-Schwartz, S., Frank, E., Anderson, B., Hlatala, S. A., Luther, J. F., Sherrill, J. T., ... Kupfer, D. J. (2000). Social rhythm disruption and stressful life events in the onset of bipolar and unipolar episodes. *Psychological Medicine*, 30, 1005–1016. doi:10.1017/S0033291799002706
- Malkoff-Schwartz, S., Frank, E., Anderson, B., Sherrill, J. T., Siegel, L., Patterson, D., & Kupfer, D. J. (1998). Stressful life events and social rhythm disruption in the onset of manic and depressive bipolar episodes. *Archives of General Psychiatry*, 55, 702–707. doi:10.1001/archpsyc.55.8.702
- McClung, C. A., Sidiropoulou, K., Vitaterna, M., Takahashi, J. S., White, F. J., Cooper, D. C., & Nestler, E. J. (2005). Regulation of dopaminergic transmission and cocaine reward by the Clock gene. *Proceedings of the National Academy of Sciences USA*, 102, 9377–9381. doi:10.1073/pnas.0503584102
- McPherson, H., Herbison, P., & Romans, S. (1993). Life events and relapse in established bipolar affective disorder. *British Journal of Psychiatry*, 163, 381–385. doi:10.1192/bjp.163.3.381
- Merikangas, K. R., Akiskal, H. S., Angst, J., Greenberg, P. E., Hirschfeld, R. M., Petukhova, M., & Kessler,

- R. C. (2007). Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Archives of General Psychiatry*, *64*(5), 543–552. doi:10.1001/archpsyc.64.5.543
- Meyer, B., Johnson, S. L., & Carver, C. S. (1999). Exploring behavioral activation and inhibition sensitivities among college students at risk for bipolar spectrum symptomatology. *Journal of Psychopathology and Behavioral Assessment*, *21*, 275–292. doi:10.1023/A:1022119414440
- Meyer, B., Johnson, S. L., & Winters, R. (2001). Responsiveness to threat and incentive in bipolar disorder: Relations of the BIS/BAS scales with symptoms. *Journal of Psychopathology and Behavioral Assessment*, *23*, 133–143. doi:10.1023/A:1010929402770
- Miklowitz, D. J., & Johnson, S. L. (2006). The psychopathology and treatment of bipolar disorder. *Annual Review of Clinical Psychology*, *2*, 199–235. doi:10.1023/A:1010929402770
- Miklowitz, D. J., & Johnson, S. L. (2009). Social and familial factors in the course of bipolar disorders: Basic processes and relevant interventions. *Clinical Psychology: A Publication of the Division of Clinical Psychology of the American Psychological Association*, *16*(2), 281–296. doi:10.1111/j.1468-2850.2009.01166.x
- Mistleberger, R. E., & Skene, D. J. (2005). Nonphotic entrainment in humans? *Journal of Biological Rhythms*, *20* (4), 339–352. doi:10.1177/0748730405277982
- Morin, C. M., Rodrigue, S., & Ivers, H. (2003). Role of stress, arousal, and coping skills in primary insomnia. *Psychosomatic Medicine*, *65*, 259–267. doi:10.1097/01.PSY.0000030391.09558.A3
- Murray, G., Allen, N. B., & Trinder, J. (2002). Mood and the circadian system: Investigation of a circadian component in positive affect. *Chronobiology International*, *19*, 1151–1169. doi:10.1081/CBI-120015956
- Murray, G., & Harvey, A. (2010). Circadian rhythms and sleep in bipolar disorder. *Bipolar Disorders*, *12*, 459–472. doi:10.1111/j.1399-5618.2010.00843.x
- Murray, C. J. L., & Lopez, A. D. (1996). Evidence-based health policy—Lessons from the Global Burden of Disease Study. *Science*, *274*(5288), 740–743. doi:10.1126/science.274.5288.740
- Murray, G., Nicholas, C. L., Kleiman, J., Dwyer, R., Carrington, M. J., Allen, N. B., & Trinder, J. (2009). Nature's clock and human mood: The circadian system modulates reward motivation. *Emotion*, *9*, 705–716. doi:10.1037/a0017080
- Nusslock, R., Abramson, L. Y., Harmon-Jones, E., Alloy, L. B., & Cohen, A. N. (2009). Psychosocial interventions for bipolar disorder: Perspective from the behavioral approach system (BAS) dysregulation theory. *Clinical Psychology: Science and Practice*, *16*(4), 449–469.
- Nusslock, R., Abramson, L. Y., Harmon-Jones, E., Alloy, L. B., & Hogan, M. E. (2007). A goal-striving life event and the onset of hypomanic and depressive episodes and symptoms: Perspective from the behavioral approach system (BAS) dysregulation theory. *Journal of Abnormal Psychology*, *116*(1), 105–115. doi:10.1037/0021-843X.116.1.105
- Nusslock, R., Almeida, J. R. C., Forbes, E. E., Versace, A., Frank, E., LaBarbara, E. J., ... Phillips, M. L. (2012). Waiting to win: Elevated striatal and orbitofrontal cortical activity during reward anticipation in euthymic bipolar adults. *Bipolar Disorders*, *14*(3), 249–260. doi:10.1111/j.1399-5618.2012.01012.x
- Nusslock, R., Harmon-Jones, E., Alloy, L. B., Urosevic, S., Goldstein, K. E., & Abramson, L. Y., (2012). *Elevated left mid-frontal cortical activity prospectively predicts conversion to bipolar I disorder*. *Journal of Abnormal Psychology*. *121*(3), 592–601. doi:10.1037/a0028973
- Pardoën, D., Bauwens, F., Dramaix, M., Tracy, A., Genevrois, C., Staner, L., & Mendlewicz, J. (1996). Life events and primary affective disorders. A one-year prospective study. *British Journal of Psychiatry*, *169*, 160–166. doi:10.1192/bjp.169.2.160
- Partinen, M. (1994). Sleep disorders and stress. *Journal of Psychosomatic Research*, *38*(Suppl. 1), 89–91.
- Paykel, E. S. (2001). Stress and affective disorders in humans. *Seminars in Clinical Neuropsychiatry*, *6*(1), 4–11. doi:10.1053/scnp.2001.19411
- Paykel, E. S. (2003). Life events and affective disorders. *Acta Psychiatrica Scandinavica*, *108*(Suppl. 318), 61–66. doi:10.1034/j.1600-0447.108.s418.13.x
- Plante, D. T., & Winkelman, J. W. (2008). Sleep disturbance in bipolar disorder: Therapeutic implications. *American Journal of Psychiatry*, *165*, 830–843. doi:10.1176/appi.ajp.2008.08010077
- Post, R. M. (1992). Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *American Journal of Psychiatry*, *149*(8), 999–1010.
- Proudfoot, J., Doran, J., Manicavasager, V., & Parker, G. (2010). The precipitants of manic/hypomanic episodes in the context of bipolar disorder: A review. *Journal of Affective Disorders*, *133*(3), 381–387. doi:10.1016/j.jad.2010.10.051.

- Ronnenberg, T., & Merrow, M. (2007). Entrainment of the human circadian clock. *Cold Spring Harbor Symposia on Quantitative Biology*, 72, 293–299.
- Roybal, K., Theobald, D., Graham, A., DiNieri, J. A., Russo, S. J., Krishnan, V., ... McClung, C. A. (2007). Mania-like behavior induced by disruption of CLOCK. *Proceedings of the National Academy of Sciences USA*, 104, 6406–6411. doi:10.1073/pnas.0609625104
- Russell, S. J., & Browne, J. L. (2005). Staying well with bipolar disorder. *Australian and New Zealand Journal of Psychiatry*, 39, 187–193. doi:10.1080/j.1440-1614.2005.01542.x
- Salavert, J., Caseras, X., Torrubia, R., Furest, S., Arranz, B., Duenas, R., & San, L. (2007). The functioning of the behavioral activation and inhibition systems in bipolar I euthymic patients and its influence in subsequent episodes over an eighteen-month period. *Personality and Individual Differences*, 42, 1323–1331. doi:10.1016/j.paid.2006.10.010
- Salvadore, G., Quiroz, J. A., Mchado-Vieira, R., Henter, I. D., Manji, H. K., & Zarate, C. A., Jr. (2010). The neurobiology of the switch process in bipolar disorder: A review. *Journal of Clinical Psychiatry*, 71(11), 1488–1501. doi:10.4088/JCP.09r05259gre
- Sclare, P., & Creed, F. (1990). Life events and the onset of mania. *British Journal of Psychiatry*, 156, 509–514. doi:10.1192/bjp.156.4.508
- Shibata, S., Tahara, Y., & Hirao, A. (2010). The adjustment and manipulation of biological rhythms by light, nutrition, and abused drugs. *Advanced Drug Delivery Reviews*, 62, 918–927. doi:10.1016/j.addr.2010.06.003
- Skejelstad, D. V., Malt, U. F., & Holte, A. (2010). Symptoms and signs of the initial prodrome of bipolar disorder: A systematic review. *Journal of Affective Disorders*, 126, 1–13. doi:10.1016/j.jad.2009.10.003
- Sylvia, L. G., Alloy, L. B., Hafner, J. A., Gauger, M. C., & Verndon, K. (2009). Life events and social rhythms in bipolar spectrum disorders: A prospective study. *Behavior Therapy*, 40, 131–141. doi:10.1016/j.beth.2008.04.003
- Urosevic, S., Abramson, L. Y., Alloy, L. B., Nusslock, R., Harmon-Jones, E., Bender, R., & Hogan, M. E. (2010). Increased rates of events that activate or deactivate the behavioral approach system, but not events related to goal attainment, in bipolar spectrum disorders. *Journal of Abnormal Psychology*, 119, 610–615. doi:10.1037/a0019533doi:10.1037/a0019533
- Urosevic, S., Abramson, L. Y., Harmon-Jones, E., & Alloy, L. B. (2008). Dysregulation of the behavioral approach system (BAS) in bipolar spectrum disorders: Review of theory and evidence. *Clinical Psychology Review*, 28(7), 1188–1205. doi:10.1016/j.cpr.2008.04.004
- Watson, S., Gallagher, P., Ritchie, J. C., Ferrier, N., & Young, A. H. (2004). Hypothalamic-pituitary-adrenal axis function in patients with bipolar disorder. *British Journal of Psychiatry*, 184, 496–502. doi:10.1192/bjp.184.6.496
- Wehr, T. A. (1989). Sleep loss: A preventable cause of mania and other excited states. *Journal of Clinical Psychiatry*, 50 (Suppl. 12), 8–16.
- Wehr, T. A., Sack, D. A., & Rosenthal, N. E. (1987). Sleep reduction as a final common pathway in the genesis of mania. *American Journal of Psychiatry*, 144(2), 201–204.

Received September 23, 2011; revised April 1, 2012; accepted March 2, 2013.