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# Future Directions for Understanding Adolescent Bipolar Spectrum Disorders: A Reward Hypersensitivity Perspective

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## Abstract

The idea that bipolar spectrum disorders (BSDs) are characterized by enhanced sensitivity to rewarding stimuli is at the core of the reward hypersensitivity model, one of the most prominent and well-supported theories of BSDs. In this article, we present the reward hypersensitivity model of BSDs, review evidence supporting it, discuss its relevance to explaining why BSDs typically begin and consolidate during the period of adolescence, and consider three major unresolved issues for this model that provide important directions for future research. Finally, we present integrations of the reward hypersensitivity model with circadian rhythm and immune system models that should provide greater understanding of the mechanisms involved in BSDs, and then suggest additional directions for future research deriving from these integrated models.

Bipolar spectrum disorders (BSDs) are defined by extreme and opposite states of mood (euphoria or irritability versus sadness), motivation (excessive goal pursuit versus withdrawal and anhedonia), behavior (supercharged energy, decreased need for sleep, and increased talkativeness versus fatigue, psychomotor retardation, and lethargy), and cognition (grandiosity and racing thoughts versus worthlessness and concentration difficulties), occurring within the same individual. BSDs occur on a spectrum of severity from the milder cyclothymic disorder (involving brief periods of hypomanic and depressive symptoms), to bipolar II disorder (involving at least one hypomanic episode and at least one major depressive episode), to full-blown bipolar I disorder (involving at least one manic episode) at the most severe end of the continuum (e.g., Alloy et al., 2012b; Birmaher et al., 2009). Furthermore, milder forms of bipolar disorder sometimes progress to the more severe forms (e.g., Alloy et al., 2012b; Birmaher et al., 2009). BSDs are prevalent (Merikangas et al., 2007; Van Meter, Moreira, & Youngstrom, 2011), recurrent, and are associated with functional disability (e.g., Miklowitz & Johnson, 2006).

In this article, we begin by discussing adolescence as a period of risk for the onset and consolidation of BSDs. We then suggest that the reward hypersensitivity model of BSDs may not only help to explain the onset and course of BSDs, but also its typical onset in adolescence. We present the reward hypersensitivity model of BSDs and evidence that

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supports it. We then discuss three major unresolved issues for the reward hypersensitivity model that provide future directions for research. Finally, as additional future directions, we also present integrations of the reward hypersensitivity model with circadian rhythm models and immune system models of BSDs, respectively, that we believe will further enhance our understanding of BSDs and their typical onset in adolescence, and are ripe for further new research.

## Adolescence is an "Age of Risk" for Bipolar Spectrum Disorders

Adolescence may be a critical developmental period constituting an "age of risk" for onset and consolidation of BSDs (Alloy et al., 2006). Although BSDs occur in prepubertal children, they more commonly have their onset after puberty (e.g., Goldstein et al., 2017; Youngstrom, Birmaher, & Findling, 2008). However, recent secular trends indicate that pubertal onset may be as young as age 8 (Sorensen et al., 2012). The first peak in onset of the adult form of BSD occurs between ages 14–19 (see Alloy et al., 2006; 2012a for reviews). And, the majority of individuals with BSDs have onset of their disorder in adolescence (e.g., Bellivier et al., 2014). Moreover, adolescent onset bipolar disorder is often associated with a worse course, greater comorbidity of anxiety disorders, substance use, and ADHD, and greater family history than adult onset bipolar disorder (e.g., Birmaher et al., 2009; Post et al., 2010; but see Cicero, Epler, & Sher, 2009 for evidence of more positive outcomes). Finally, BSDs with adolescent onset are characterized by more mixed states (with hypo/manic and depressive symptoms occurring together), mood lability, greater dysphoria and irritability, greater suicidal ideation and attempts, and greater chronicity than onset in adulthood (e.g., Biederman et al., 2005; Leverich et al., 2007). That BSDs have their typical onset in adolescence suggests that there are processes that develop or change during adolescence that likely are involved in the onset of BSDs.

Although adolescence is characterized by multiple neurobiological, psychological, and social changes, two developments during adolescence may be especially relevant to understanding BSD onset during this period: maturation of the neural reward system and increased exposure to stressful life events and goal opportunities. Adolescence is a developmental period involving heightened reward sensitivity. In early adolescence, neural circuitry implicated in reward processing (Haber & Knutson, 2010) undergoes rapid development, resulting in normative increases in sensitivity to and motivation for rewards relative to children and adults (see Forbes & Dahl, 2012 and Steinberg, 2010 for reviews). Dopamine expression also increases in adolescence underlying such traits as sensation seeking and reward sensitivity (Wahlstrom, Collins, White, & Luciana, 2010).

Adolescence is also a developmental period in which youth have less parental monitoring and more autonomous control over their lives. Related to this, compared to younger children, adolescents engage in greater exploration, more risk-taking behaviors (both positive and negative), and have increased opportunities for goal-striving (e.g., Baumrind, 1987; Romer, Reyna, & Pardo, 2016). And, perhaps as a consequence of this increased exploration and goal-striving, the period of adolescence also is associated with large increases in experiences of stressful life events (e.g., Ge et al., 1994).

From a reward hypersensitivity perspective on BSDs, the combination of enhanced reward sensitivity related to maturation of the neural reward system and increased exposure to goal-striving opportunities and stressors in adolescence may explain why BSDs typically have their onset during this developmental period. In the context of these normative increases in reward sensitivity and goal-striving, those individuals who have particularly high responsivity to incentives and rewards and who are exposed to high levels of goal-seeking or goal failures may be likely to develop a first onset of BSD during adolescence. Thus, next we describe the reward hypersensitivity model of BSDs and the evidence that supports it.

## Reward Hypersensitivity Model of Bipolar Spectrum Disorders: Theory and Evidence

### The Reward System

Reward sensitivity refers to the strength of approach motivation for the pursuit of desired rewards and goals in the environment and the processing of those rewards. Although multiple brain regions respond to reward, the fronto-striatal neural circuit is at the core of the reward system (e.g., Haber & Knutson, 2010). This circuit involves dopaminergic projections from midbrain nuclei (e.g., the ventral tegmental area) to subcortical regions that are central to processing the rewarding properties of stimuli (e.g., the ventral striatum [VS], including the nucleus accumbens) to target regions in the cortex (e.g., the orbitofrontal cortex [OFC], medial prefrontal cortex, anterior cingulate cortex). Both animal and human studies highlight the central role that this circuit plays in reward-responsivity, incentive-based learning, assessing probability of reward receipt, prediction error, and goal directed behavior. Whereas activation or up-regulation of the reward system leads to emotions such as happiness and elation, and enhanced approach motivation and goal-striving, deactivation or down-regulation of this system leads to sadness and anhedonia, and decreased motivation and goal-related cognitions. Connectivity analyses highlight a functional and structural coupling between the VS and OFC (Damme, Young, & Nusslock, 2017; Di Martino et al., 2008) that is sensitive to individual differences in reward sensitivity (e.g., Simon et al., 2010). Finally, stimulating midbrain dopamine neurons via optogenetics drives activation in the VS and reward-seeking behaviors (Ferenczi et al., 2016). This suggests that neuroimaging metrics of reward-related brain function are sensitive to dopaminergic signaling, which, among other neurotransmitters, has been implicated in the pathophysiology of mood disorders (Nusslock & Alloy, 2017).

### The Reward Hypersensitivity Model of BSDs

According to the reward hypersensitivity model of BSDs (e.g., Alloy, Olino, Freed, & Nusslock, 2016; Depue & Collins, 1999; Johnson, Edge, Holmes, & Carver, 2012; Nusslock & Alloy, 2017; Urošević, Abramson, Harmon-Jones, & Alloy, 2008), vulnerability to first onset and recurrent mood episodes in BSDs is characterized by hypersensitivity to goal- and reward-relevant cues. This reward hypersensitivity can lead to excessive approach-related affect and behavior in response to life events that activate the reward system (i.e., reward-activation events [Rew-A]), such as goal-striving or attainment events (e.g., working toward or receiving a job promotion). In the extreme, this excessive increase in approach motivation

is reflected in hypo/manic symptoms, such as elevated mood, decreased need for sleep, increased psychomotor activation, extreme energy, self-confidence, and pursuit of rewarding activities without attention to risks (see red pathway in Figure 1). Likewise, hypersensitivity to rewards also can lead to excessive deactivation or down-regulation of approach-related affect and motivation when individuals encounter reward-deactivation events (Rew-D) involving definite failures, losses, or nonattainment of goals. Such excessive reward system deactivation is reflected in depressive symptoms, such as decreased goal-directed activity, decreased energy, loss of interest or anhedonia, psychomotor retardation, hopelessness, and sadness (see blue pathway in Figure 1). The logic here is that reward hypersensitivity should make individuals hypersensitive to cues signaling both the possible attainment and loss of reward, and that in the face of loss, individuals with reward hypersensitivity should be at increased risk for depression given the high value they place on rewards. If the reward loss is perceived to be remediable and merely a temporary obstacle on the path to reward attainment, it should activate approach motivation and trigger anger/irritability symptoms of hypo/mania (e.g., Carver & Harmon-Jones, 2009; see Goldstein et al., 2017 for a discussion of rage in youth BSD). Finally, it is important to emphasize that the hypothesized vulnerability to BSDs in this model is a tendency toward excessive reward system activation and deactivation, not the actual activation or deactivation (dysregulation) itself, which is considered the more proximal precursor of specific mood symptoms/episodes.

The model also contains a transactional component in which individuals who have high reward sensitivity may engage in behaviors that lead them to be exposed to goal- or reward-relevant events more frequently via “stress generation” processes (Hammen, 1991), as well as responding more strongly to these events when they occur. Thus, the theory is a “two-hit” model in which vulnerable, reward-hypersensitive people have greater exposure to the very goal- and reward-relevant events that trigger excessive responses from their reward systems.

## Evidence for the Reward Hypersensitivity Model in Bipolar Spectrum Disorders

Considerable evidence across multiple levels of analysis, including self-report, behavioral, cognitive, life event, neurophysiological (i.e., electroencephalographic [EEG]), and neural (functional magnetic resonance imaging [fMRI]), supports the reward hypersensitivity model of BSDs (see Alloy, Nusslock, & Boland, 2015b; Alloy et al., 2016 and Nusslock & Alloy, 2017 for recent reviews). Individuals with or vulnerable to BSDs based on either family history or behavioral risk exhibit ambitious goal-striving, and display greater self-reported, behavioral, emotional, cognitive, neurophysiological, and neural responses to rewards than controls (see Alloy et al., 2015b; 2016, Nusslock & Alloy, 2017 for comprehensive reviews).

Studies of individuals with BSDs in a euthymic state can address whether the high reward sensitivity shown to be associated with BSDs is a mood-independent trait or tied to current mood state. Such studies tend to support the trait hypothesis. Currently euthymic individuals with a BSD exhibit higher self-reported reward sensitivity and increased behavioral and neuro-physiological responses to rewards on reward-related tasks (see Alloy et al., 2016; Nusslock & Alloy, 2017 for reviews). In addition, fMRI studies employing reward task paradigms provide support for elevated VS and OFC reward responses in both manic and

euthymic individuals with bipolar I and II disorders, and individuals at risk for BSD (see Alloy et al., 2016; Nusslock & Alloy, 2017 for reviews; but see Yip et al., 2015 and Schreiter et al., 2016 for alternative findings). Using diffusion imaging, Damme et al. (2017) found that individuals at risk for BSD also show enhanced cortico-striatal structural connectivity compared to low-risk individuals. It is important to note, however, that MRI is largely a descriptive technique, and thus, unable to establish the causal influence of neural regions in the pathophysiology of BSDs. Future research using neuromodulatory techniques (e.g., TMS), pharmacology, and lesion methods in animals and humans is needed to better address this issue.

Consistent with the hypothesis that reward hypersensitivity is a vulnerability for onset and recurrences of bipolar mood episodes, a few prospective studies have found that high self-reported, behavioral, and/or neurophysiological reward sensitivity prospectively predicts greater likelihood of developing first lifetime onset of BSD in an adolescent sample with no prior BSD history (Alloy et al., 2012a), recurrent BSD mood episodes in a young adult sample with bipolar II or cyclothymia (Alloy et al., 2008), and of progressing to bipolar I disorder among the young adults with bipolar II or cyclothymia (Alloy et al., 2012b; Nusslock et al., 2012).

The reward hypersensitivity model of BSDs also predicts that Rew-A events, involving goal striving, goal attainment, or goal obstacles evoking anger and irritability, should trigger hypo/manic episodes, whereas Rew-D events, involving failures or losses that cannot be remediated, should trigger depressive episodes. Consistent with this hypothesis, Rew-A events, but not positive events in general, have been found to predict hypo/manic symptoms or episode onsets among individuals with BSDs (see Alloy et al., 2015b; 2016 for reviews). In addition, events that tend to provoke anger, theorized to also activate the reward system, also predict hypomanic symptoms (e.g., Carver, 2004; Harmon-Jones et al., 2002). On the other hand, evidence suggests that Rew-D events (e.g., failures or losses) may precipitate depressive episodes (see Alloy et al., 2015b; 2016 for reviews). There is also evidence for the transactional component of the reward hypersensitivity model. Individuals with BSDs (Urošević et al., 2010) as well as those with high self-reported reward sensitivity (Boland et al., 2016) experience elevated rates of Rew-A and Rew-D events over follow-up compared to healthy controls and moderate reward sensitive individuals, respectively, and these higher rates of reward-relevant events predict hypo/manic and depressive symptoms prospectively (Boland et al., 2016).

In summary, the reward hypersensitivity model of BSDs is relatively well-supported (see Alloy et al., 2015b; 2016; Nusslock & Alloy, 2017 for more comprehensive reviews) and provides a useful perspective on understanding the onset and course of BSDs, particularly during the vulnerable period of adolescence. Indeed, at a time when there are normative increases in reward sensitivity and exposure to goal-striving opportunities, the reward model may help to explain why those individuals who have particularly high sensitivity to incentives and who are exposed to especially high levels of goal-seeking or goal failures are likely to develop a first onset of BSD during adolescence. The model also may be relevant to understanding the high rates of comorbidity between BSDs and substance use disorders during adolescence. Inasmuch as elevated reward sensitivity leads to approach behavior

toward rewarding stimuli, and drugs of abuse have such rewarding properties, this perspective proposes that reward hypersensitivity should lead to greater substance use and risk for addiction. And, indeed, there is some evidence that high self-reported or behavioral reward sensitivity is associated with and predictive of elevated substance use and substance use disorders (see Alloy et al., 2009 for review).

## Future Directions: Unresolved Issues in the Reward Hypersensitivity Model of Bipolar Spectrum Disorders

Although the reward hypersensitivity model has been quite successful in explaining many features of BSD and its onset and course, it also faces certain challenges and unresolved issues. These unresolved issues are ripe for additional research efforts, which we turn to in this section.

### Bipolar Depression – Reward Hyper- or Hypo-sensitivity?

According to the reward hypersensitivity model of BSDs, individuals who are hyper-reactive to reward-relevant cues should be likely to become depressed when their reward systems become excessively deactivated following exposure to life events involving irreconcilable failures and losses (goal failures). However, to date, there is less consistent evidence for the role of reward hypersensitivity in bipolar depression than in bipolar hypo/mania (see Alloy et al., 2016; Nusslock & Alloy, 2017). Moreover, the fact that much evidence supports the role of blunted reward sensitivity and processing in unipolar depression (see Alloy et al., 2016; Nusslock & Alloy, 2017 for reviews) naturally raises the question of whether depressive episodes within BSDs are characterized by reward hyper- or hypo-sensitivity.

It is possible that reward hypersensitivity predicts only some symptoms of bipolar depression specifically, such as anhedonia and motivational deficits, when individuals experience irreconcilable losses or failures to obtain desired goals. Thus, studies that examine the relationship between reward processing and bipolar depression as a whole may yield mixed findings because the specific association between reward hypersensitivity and specific depressive symptoms is obscured. Another possibility is that different processes contribute to bipolar depression, unipolar depression, and hypo/mania. Whereas reward hypersensitivity may lead to bipolar hypo/mania, bipolar depression may be the result of different etiological processes (e.g., threat sensitivity) than those important in unipolar depression (e.g., blunted reward sensitivity). However, there does not appear to be clear distinctions in the symptom profiles of unipolar versus bipolar depression, or in how anhedonia is expressed in these two disorders (see Cuellar, Johnson, & Winters, 2005 for review). Moreover, even unipolar depression is associated with elevated reward processing in some structures of the neural reward circuit. A recent meta-analysis (Ng et al., 2018) indicates that whereas individuals with unipolar major depressive disorder exhibit blunted reward processing in the VS, they show elevated responses to reward in the OFC. Clearly, further research is needed to test these competing hypotheses and uncover whether depressive phases of BSDs are better characterized by hyper- or hypo-reward sensitivity and whether they are similar or different from unipolar depression.

## Reward Hypersensitivity as a Risk Factor for a Specific Subset of Bipolar Symptoms

Research on the reward hypersensitivity model has tended to consider bipolar disorder as a unitary illness. There is a growing chorus of scientists, however, arguing that psychology and psychiatry need to move beyond considering mental illnesses as homogenous constructs and instead examine the relationships between specific mechanisms and specific symptoms (e.g., Insel & Cuthbert, 2015). We (Nusslock & Alloy, 2017) agree and suggest that an important direction for future research is to assess the role of reward hypersensitivity in specific clusters of hypo/manic and depressive symptoms. Here we outline our predictions for this needed research.

With respect to hypo/mania, we predict that reward hypersensitivity will be most strongly associated with symptoms characterized by excessive approach motivation, specifically, elevated energy, increased goal-directed activity, decreased need for sleep, increased confidence, and irritability when goal-pursuit is thwarted (but see Stringaris, Stahl, Santosh, & Goodman, 2011 for an alternate classification of hypo/manic symptoms). We base this prediction on the strong convergence between the characteristics of these symptoms and elevated reward-related neural activation, which is characterized by increased approach motivation, reward sensitivity, and goal pursuit. Reward processing and approach motivation have not been directly implicated in cognitive activity (Alloy et al., 2015b), and thus, hypo/manic cognitive symptoms involving distractibility and flight of ideas, should be less related to reward hypersensitivity than the proposed cluster of approach-related hypo/manic symptoms. Decreased need for sleep is included in this cluster of approach-related hypo/manic symptoms, given the coupling of reward processing and approach motivation with sleep variables, circadian influences, and circadian genes (see Alloy et al., 2015b; 2016 for reviews). Increased confidence is included in this cluster, given that elevated reward sensitivity, approach motivation, and BSDs are linked with elevated confidence following goal-attainment (e.g., Eisner et al., 2008; Johnson & Jones, 2009). Irritability is included because of the neurobiological overlap between anger and approach motivation (Harmon-Jones, 2003; Carver & Harmon-Jones, 2009) and the increase in approach-related neural activity if goal-pursuit is thwarted (Harmon-Jones, 2003).

As discussed, there is still debate about the involvement of reward hypersensitivity in the pathophysiology of bipolar depression. Thus, our predictions about the specific symptoms of bipolar depression associated with reward hypersensitivity are more tenuous. However, the reward hypersensitivity model has predicted that a hypersensitivity to rewards leads to excessive down-regulation of approach motivation when individuals encounter Rew-D events. Thus, reward hypersensitivity should be associated with symptoms centering on motivational deficits (e.g., anhedonia, reduced goal-directed behavior and appetitive motivation, and psychomotor deactivation) and less so on cognitive symptoms. Support for this prediction comes from research implicating abnormalities in the fronto-striatal circuit in motivational deficits, and anhedonia in particular (e.g., Nusslock & Alloy, 2017; Treadway, 2016). Future research is needed to test these predictions.

### Bipolar Mixed States

As mentioned above, mixed states, in which both hypo/manic and depressive symptoms seem to occur together, along with mood lability, may be more common in adolescent onset BSDs. From the perspective of the reward hypersensitivity model, mixed states may be a misnomer and actually may be cases of affective instability with rapid changes between hypo/manic and depressive symptoms, rather than the simultaneous occurrence of both types of symptoms. Individuals with highly sensitive reward systems may show considerable lability in approach motivation and reward processing, exhibiting elevated upregulation of their reward systems and hypo/manic symptoms in response to goal opportunities or rewards and elevated downregulation of their reward systems and depressive symptoms in response to definitive goal failures and losses that occur within the same day. Theoretically, reward hypersensitive individuals will be likely to exhibit excessive approach motivation in response to Rew-A life events, become hypo/manic and take on unrealistic challenges, and thus, be more likely to then experience failure followed by depression, potentially leading to rapid switches between hypo/mania and depression within a short time interval. However, this potential explanation of seemingly mixed states has not been tested. Ecological momentary assessment (EMA) research designs could be valuable in testing this hypothesis.

An alternative explanation for bipolar mixed states from the reward hypersensitivity perspective may be related to chronometry of reward system responses. Urošević et al. (2008) proposed that individuals with hypersensitive reward systems not only show greater intensity (higher peaks and lower troughs) of responses to perturbations of their reward systems, but also may exhibit dysregulated chronometry of their reward responses, such as a faster rise to peak response and longer time to recovery to baseline. If this hypothesis were extended to include the possibility that the different affective, behavioral, cognitive, and neural components of the response to anticipation or receipt of rewards typically operated with different time courses (i.e., some components of the response are faster than others in rising to a peak and returning to baseline), then mixed hypo/manic and depressive symptoms might result. That is, as some components of excessive reward system activation and accompanying hypo/manic symptoms resolve and return to low levels of activation more quickly than others, depressive symptoms that may be related to these components of the reward response may begin to occur, leading to the simultaneous occurrence of some hypo/manic and some depressive symptoms. Studies that simultaneously examine the time courses of affective, behavioral, cognitive, and neural responses to reward-relevant stimuli while also assessing mood symptoms may shed some light on the dysregulated reward chronometry hypothesis of mixed states.

Clearly, research is needed to test these reward hypersensitivity model – relevant hypotheses about the bases of mixed states in BSDs, as well as to explore other mechanisms that may account for such mixed states. The seemingly overlapping occurrence of some hypo/manic and depressive symptoms in some individuals with BSDs is a challenge for further investigation.

## Future Directions: Understanding Mechanisms of Reward Hypersensitivity in Bipolar Spectrum Disorders Through Integration with Other Models

In disorders as complex and multi-faceted as BSDs, it is unlikely that one theoretical approach on its own will fully explain the mechanisms underlying the onset and course of both poles of the disorders. Thus, an integration of the reward hypersensitivity model with other models of BSDs may suggest promising avenues for further research that will lead to a more comprehensive understanding of these conditions. We suggest that integrated reward-circadian and reward-immune models of BSDs may provide fertile grounds for further explaining BSDs.

### Integrating Reward Hypersensitivity and Circadian Models of BSDs

**The Circadian System.—**Biological processes that repeat about every 24 hours and persist with the same period in the absence of external cues are defined as “circadian rhythms” (Czeisler & Gooley, 2007). The suprachiasmatic nucleus (SCN), or “biological clock”, in the anterior hypothalamus regulates central circadian rhythms (e.g., Czeisler & Gooley, 2007; Reppert & Wever, 2001), which are entrained predominately by the external zeitgeber (“time giver”), light (e.g., Panda, Hogenesch, & Kay, 2002; Wever, 1989). Circadian rhythms also can be entrained or phase-shifted by nonphotic cues, including social or auditory stimuli, exercise, and daily schedules or social rhythms (e.g., Ehlers, Frank, & Kupfer, 1988; Goel, 2005; Grandin, Alloy, & Abramson, 2006; Mistlberger & Skene, 2004). The sleep/wake cycle, body temperature, cortisol, neurotransmitters, and melatonin all show circadian rhythms (Reppert & Wever, 2001), with melatonin considered the most accurate physiological marker of endogenous circadian function (Lewy & Sack, 1989).

**Circadian Rhythm Models of BSDs.—**Circadian rhythm disruption has been proposed to be a key mechanism in the neurobiological vulnerability to BSDs (e.g., Alloy, Ng., Titone, & Boland, 2017; Ehlers et al., 1988; Grandin et al., 2006; McClung, 2007; Murray & Harvey, 2010). Many individuals with BSDs have alterations in circadian rhythms of sleep-wake, activity, melatonin and other hormones even in euthymic periods (e.g., McClung, 2007; Murray & Harvey, 2010; see Alloy et al., 2015b; 2017 for recent reviews). Individuals with chronic hypomanic symptoms also show activity rhythm irregularities as measured by actigraphy and self-report. In addition, core clock genes involved in the regulation of circadian rhythms are altered in BSDs (e.g., see Alloy et al., 2015b; 2017 for comprehensive reviews ).

Dysregulation of circadian rhythms may arise either from intrinsic abnormalities of the SCN’s pacemaking control over bodily functions, or from dysfunction in the entrainment of the SCN by external zeitgebers (Grandin et al., 2006). The social zeitgeber theory (Alloy et al., 2015b; 2017; Ehlers et al., 1988; Grandin et al., 2006) approaches understanding of BSDs from this latter perspective. According to this theory, life events that disrupt social zeitgebers, i.e., daily social rhythms or schedules (e.g., bedtimes, mealtimes, start of school), precipitate mood symptoms by disturbing circadian rhythms. Social rhythm disrupting (SRD) events (e.g., change in bedtime) may be associated with increased light exposure, which can phase shift melatonin and other circadian rhythms (Roenneberg & Merrow, 2007;

Wever, 1989), or may disrupt circadian rhythms through their effects on non-photic zeitgebers (Goel, 2005).

Consistent with the social zeitgeber theory (see Alloy et al., 2015b; 2017 for extensive reviews of this evidence), individuals with BSDs exhibit less social rhythm regularity than controls, and this irregularity predicts greater variability in mood symptoms and shorter time to onset of bipolar hypo/manic and depressive episodes. Among individuals with BSDs, SRD events are more likely to occur prior to manic or depressive episodes relative to control periods, and an increase in SRD events predicts a shorter time to onset of major depressive episodes. Individuals with BSDs also are more susceptible than controls to experiencing SRD in response to life events of similar magnitude and valence (Boland et al., 2012). Finally, the efficacy of treatments involving social rhythm stabilization for patients with BSDs also provides some support for the social zeitgeber theory (e.g., Frank et al., 2005). Although these findings support concurrent and prospective associations between SRD and bipolar symptoms/episodes, as yet, there is no direct evidence that SRD leads to mood symptoms via disruption of circadian rhythms. Future research is needed to test this proposed circadian mechanism.

**Integrated Reward-Circadian Model.—**Although reward and circadian approaches to BSDs mostly have proceeded independently of each other, there is growing evidence that the SCN and dopamine-mediated cortico-striatal circuitry involved in reward processing are bidirectionally related (see Alloy et al., 2015b and Murray et al., 2009 for reviews). Indeed, cortico-striatal reward areas exhibit time-of-day or circadian activation effects (e.g., Byrne et al., 2017; Hasler, Forbes, & Franzen, 2014), circadian clock genes are expressed in many brain reward areas (e.g., Forbes et al., 2012; Sleipness, Sorg, & Jansen, 2007), and a direct functional connection exists from midbrain dopamine neurons to the SCN in rodents (Grippo et al., 2017).

Based on these bidirectional associations between the reward and circadian systems, Alloy et al. (2015b) proposed an integrated reward circadian rhythm (RCR) model of BSDs (Figure 2). According to this integrated model, in vulnerable reward hypersensitive individuals, Rew-A and Rew-D events lead to excessive reward activation and deactivation states, respectively, which, in turn, directly and indirectly (through behaviors that generate social rhythm disrupting [SRD] events) lead to circadian rhythm disruption (see green boxes in Figure 2). Via the indirect pathway through SRD events, when reward hypersensitive individuals experience excessive reward activation in response to goals or rewards, they should exhibit excessively high appetitive motivation, goal-striving, and response initiation (Alloy et al., 2015b; Nusslock, Abramson, Harmon-Jones, Alloy, & Coan, 2009), all incongruent with maintaining regular social rhythms. Thus, they may work excessively long hours and neglect normal social routines (e.g., bedtime), which, in turn, may disrupt circadian rhythms and trigger hypo/manic symptoms. Similarly, in vulnerable individuals, Rew-D events (e.g., goal failure) can lead to excessive reward system deactivation involving decreased approach and response initiation and disregard of social routines. The change in social routines should disrupt circadian rhythms and lead to depressive symptoms.

There may be reciprocal influences as well. In the opposite causal direction, disruption of circadian rhythms, in turn, may influence levels of reward activation (see yellow feedback path, Figure 2). Reward system activation may be partly influenced by SCN timing information (e.g., Murray et al., 2009; Sleipness et al., 2007) and by SRD events that alter circadian rhythms. Consistent with this idea, studies show circadian influences on reward motivation in animals (Murray et al., 2009) and self-reported positive affect in humans (e.g., Miller et al., 2015; Murray et al., 2009), and there are time-of-day effects on cortico-striatal reward responsiveness in humans (e.g., Byrne et al., 2017; Hasler et al., 2014).

An integrated RCR model also may be relevant to understanding why BSDs frequently begin and consolidate during adolescence. Adolescence is characterized by sleep timing changes, including a delay of bedtimes and irregular sleep schedules (e.g., Carskadon, 2011; Knutson, 2005; Phillips et al., 2017), and a phase shift of the melatonin and other circadian rhythms (Carskadon, Vieira, & Acebo, 1993). In addition, in adolescence, an increase in screen time use (e.g., computer, cell phone, social media) occurs, which is associated with disturbances in sleep duration and delayed timing (e.g., Hale & Guan, 2015). Electronic screens emit blue light, which can signal blue-light sensitive melanopsin in photo-responsive retinal ganglion cells that it is daytime, and, in turn, delay melatonin onset (Henriksen et al., 2016). The adolescent increase in screen usage may act as a SRD event and contribute to BSD mood episodes, and indeed, elevated screen use is associated with depression (e.g., Gunnell et al., 2016). Moreover, blue-light blocking glasses are a promising adjunctive treatment for BSD (Henriksen et al., 2016). Thus, consideration of circadian as well as reward mechanisms may better account for why BSDs are likely to emerge in adolescence. In addition, these normative changes in sleep timing and circadian rhythms during adolescence also may help to explain some BSD symptoms, such as sleep disturbances, mood swings, and changes in concentration and cognitive functioning, which are influenced by circadian rhythm disturbance (Alloy et al., 2015b).

Consistent with the integrated RCR model, Alloy, Boland, Ng, Whitehouse, and Abramson (2015a) found that the combination of reward hypersensitivity and low social rhythm regularity predicted first lifetime onset of BSD in adolescents better than reward hypersensitivity alone. In a further test of the integrated RCR model, Boland et al. (2016) found that adolescents with high reward sensitivity generated more Rew-A and Rew-D events (via “stress generation”), and experienced more interviewer-rated SRD from these events, than moderate reward sensitivity adolescents, controlling for mood symptoms and initial social rhythm regularity. Moreover, these Rew-A and Rew-D events predicted prospective increases in hypo/manic and depressive symptoms, respectively, mediated by increases in SRD, with these reward-relevant events – SRD – mood symptom pathways stronger for the high than the moderate reward sensitivity adolescents (Boland et al., 2016).

**Future Directions for the Integrated Reward-Circadian Model.—**Although initial findings testing the RCR model are very promising, future research is needed to understand how the reward and circadian systems interact to explain BSD features, onset, and course. For example, studies that investigate the behavioral, neural, and neurobiological mechanisms underlying reciprocal interactions between the two systems are needed. In addition, only two prospective studies (Alloy et al., 2015a; Boland et al., 2016) of the integrated RCR model’s

predictions for bipolar mood episodes or symptoms have been published and these two studies only examine interactions between reward sensitivity, reward-relevant events, and social rhythms, but not circadian rhythms directly, in predicting mood symptoms/episodes. Thus, future work is needed to examine whether circadian rhythm disruption mediates the effects of reward hypersensitivity and Rew-A or Rew-D events on mood outcomes. Similarly, studies should examine whether associations between social and circadian rhythm disturbances and mood symptoms or episodes are, in turn, mediated by changes in reward system activation. Additionally, studies that involve investigating how manipulations of the reward system affect changes in circadian rhythms and vice versa should be conducted. Finally, EMA studies that assess reward sensitivity/motivation, reward-relevant events, social and circadian rhythm disruption, and hypo/manic and depressive symptoms in a fine-grained manner with temporal precision could shed much light on how the reward and circadian systems interact to predict bipolar symptoms. This work not only will inform our understanding of the etiology of BSDs, but also facilitate treatment refinement. For example, understanding the dynamic relationship between Rew-A and Rew-D events with social and circadian rhythm disruption can aid practitioners in helping clients maintain regular social/circadian rhythms in the face of such events (Nusslock et al., 2009).

## Integrating Reward Hypersensitivity and Immune System Models of BSDs

In addition to circadian dysregulation, individuals with BSDs exhibit higher peripheral inflammation (Goldsmith et al., 2016; Hamdani et al., 2013). Inflammation is highly adaptive in the short term, accelerating pathogen removal and wound healing (Irwin & Cole, 2011). However, when chronic, inflammation contributes to adiposity, insulin resistance, and other predisease states, generating risk for mental and physical health problems across the lifespan (e.g., Goldstein et al., 2015; Nusslock & Miller, 2016). Consistent with this perspective, individuals with BSDs exhibit high comorbidity with inflammation-related medical disorders, including metabolic syndrome, stroke, and heart disease (Hamdani et al., 2013). BSD also is associated with elevated childhood adversity (Kessler et al., 2010), another driving force in generating chronic inflammation given the influence of stress biology on sensitizing immune cells that initiate and sustain inflammation (Nusslock & Miller, 2016).

Research on reward function and inflammatory signaling in BSDs also has proceeded in parallel; however, growing evidence indicates bidirectional associations between reward responsivity and peripheral inflammation (Nusslock & Miller, 2016). In this section, we examine potential mechanisms underlying reward hypersensitivity and elevated inflammation in BSDs. We expand our focus here to include unipolar depression, and propose an integrated reward-immune model of the entire mood spectrum with the hope of facilitating future research.

### Reward-to-Immune Pathway: Role of Behaviors that Promote Inflammation.—

Whereas BSDs are associated with reward hypersensitivity, self-report, behavioral, neurophysiological, and neural evidence indicates that risk for unipolar depression (without a history of hypo/mania) is characterized by blunted reward sensitivity (see Alloy et al., 2016 and Nusslock & Alloy, 2017 for reviews). This suggests that risk for unipolar

depression and BSDs are characterized by distinct and opposite profiles of reward processing and reward-related brain function.

Meta-analyses (e.g., Goldsmith et al., 2016) indicate that individuals with unipolar depression exhibit elevated peripheral inflammatory biomarkers such as interleukin-6 (IL6) and c-reactive protein (CRP) and impactful inflammatory models of depression have emerged (e.g., Raison & Miller, 2013; Slavich & Irwin, 2014). Animal and human research indicates that low reward sensitivity and reduced reward-related brain function – risk factors for unipolar depression - are associated with elevated peripheral inflammation (see Felger & Treadway, 2017 for review). By contrast, individuals with reward hypersensitivity and increased reward-related brain function – risk factors for BSDs - also display elevated inflammation (e.g., Irwin & Eisenberger, 2017; Lasselin et al., 2017; Miller & Wrosch, 2007; Muscatell et al., 2016). This suggests a possible curvilinear relationship between reward sensitivity and inflammation, in which both low and high reward sensitive individuals display elevated inflammation. If true, this raises the question: How is it that both extremely low and high reward sensitivity are associated with increased inflammation? We propose that one potential mechanism is that both individuals with reward hypo- or hyper-sensitivity are more likely to engage in behaviors that promote inflammation, including substance use, consuming a high-fat/high-sugar diet, reward-relevant event generation, and, among individuals with reward hypersensitivity, excessive goal pursuit.

Both blunted (e.g., Buchel et al., 2017; Volkow, Koob, & McLellan, 2016) and elevated (e.g., Alloy et al., 2009; Gearhardt et al., 2011) reward sensitivity may lead to increased substance use and food consumption that promote inflammation (perhaps through obesity, a primary driver of inflammation, Thomas & Apovian, 2017). According to the reward deficiency model of addiction, persons with low reward sensitivity self-medicate negative affect and/or induce positive affect through high-risk addictive behaviors (e.g., Volkow et al., 2012). Consistent with this idea, blunted dopamine signaling in the VS is involved in drug and alcohol use, as well as food seeking and obesity (see Volkow et al., 2012 for review). By contrast, a reward hypersensitivity perspective on substance use suggests that elevated reward sensitivity leads to excessive approach behavior toward rewarding stimuli, including drugs of abuse and high-fat foods (see Alloy et al., 2009 for review). In line with this logic, studies report associations between reward hypersensitivity and increased substance use and food consumption (e.g., Alloy et al., 2009; Gearhardt et al., 2011).

Another proposed inflammation promoting behavior is the self-generation of stressful life events. Individuals with either reward hypo- or hyper-sensitivity are more likely to self-generate goal failures and losses (Boland, et al., 2016). These events likely activate stress biology, which has been shown to increase inflammation (Nusslock & Miller, 2016). Relatedly, individuals who exhibit excessive goal-striving tendencies or have difficulty disengaging from unattainable goals, traits previously found in adolescents at risk for BSDs (e.g., Alloy et al., 2012a), displayed higher levels of pro-inflammatory cytokines both cross-sectionally and longitudinally (Miller & Wrosch, 2007). Furthermore, both reward hypersensitive individuals and those with a BSD also self-generate excessive goal-striving events (e.g., Urosevic et al., 2010), which also can elevate inflammation (Miller & Wrosch, 2007). Thus, we hypothesize that inflammation promoting behaviors may partially mediate

the proposed curvilinear relationship in which both individuals with extremely low and high reward sensitivity display elevated inflammation (see Figure 3).

**Immune-to-reward pathway.—**Research also shows that peripheral inflammation can spread to the brain through multiple mechanisms (e.g., active transport, leaky regions of the blood-brain barrier) and modulate reward-related fronto-striatal circuitry (Nusslock & Miller, 2016). Most studies of inflammation's effects on reward function suggest that it is associated with blunted reward sensitivity. In animals, inflammatory products reduce sensitivity to rewarding stimuli and increase tolerance to the reinforcing properties of several drugs (Dantzer et al., 2008). Human studies find that manipulations that increase inflammation (e.g., endotoxin administration) lead to reduced VS activation in response to monetary rewards (Capuron et al., 2012; Eisenberger et al., 2010). However, some recent studies provide clues about conditions under which inflammation may lead to elevated reward responsivity, relevant to hypo/manic symptom occurrence. Endotoxin administration (causing acute inflammation) predicts increased behavioral effort for monetary reward when reward probability is high (Lasselin et al., 2017) and enhanced VS activation in response to social rewards (Inagaki et al., 2015; Muscatell et al., 2016). Thus, inflammation may down- or up-regulate approach motivation and reward responsivity, depending on the adaptiveness of the reward response for the situation.

Consideration of immune as well as reward mechanisms also may aid in explaining why BSDs and unipolar depression both are likely to emerge in adolescence. Immune system competence increases from infancy/childhood to adulthood and then declines in older age (Simon, Hollander, & McMichael, 2015), suggesting that adolescence is a developmental period when the immune system 'hits its stride.' The normative increases in reward sensitivity and exposure to stressful life events in adolescence combined with relatively good immuno-competence may enhance adolescents' inflammatory reactions to stressful events (Slavich & Irwin, 2014), and thus, vulnerability to depression and BSD related to elevated stress-reactive inflammation. In addition, integrating the immune model with the reward model also may help to explain some symptoms of depression and BSD in addition to those explained by reward hypersensitivity, such as anhedonia, anorexia, fatigue, and changes in cognitive functioning, which are all influenced by inflammation (e.g., Dantzer et al., 2008; McAfoose & Baune, 2009).

**Future Directions for an Integrated Reward and Immune Model of the Mood Spectrum.—**An important future direction for research on reward sensitivity is to examine bidirectional associations of reward function and inflammation with each other and as determinants of risk for the full spectrum of mood disorder symptoms, from unipolar depression to BSDs. We propose that inflammation promoting behaviors partially mediate the relationship between abnormally high or low reward sensitivity and elevated peripheral inflammation. Further, inflammatory mediators are able to access the brain, where they directly modulate cortico-striatal reward circuits. Over time, dysregulation in reward and immune signaling may synergize to form a positive feedback loop whereby dysregulation in each system exacerbates dysregulation in the other. We propose that elevated inflammation combines with low reward sensitivity to elevate risk for unipolar depression symptoms, and

with high reward sensitivity to elevate risk for BSD symptoms. Future multiwave longitudinal research that tracks reward and inflammatory signaling at multiple levels of analysis (self-report, behavioral, neural) across time is needed to test these hypotheses. Identifying reward-immune pathways in the etiology of BSDs could facilitate the generation of novel behavioral and biological neuroimmune interventions that target brain-to-immune and/or immune-to brain signaling to treat, and ideally prevent, BSD symptoms.

We further acknowledge that the circadian and immune systems also exhibit bidirectional associations. Circadian clocks control immune functions; and conversely, immune challenges and mediators affect circadian rhythms at the behavioral, cellular, and molecular levels (e.g., Cermakian et al., 2013). Thus, although it is beyond the scope of the current article, future work also should elaborate and test an integrated reward-circadian-immune model of BSDs.

## Conclusions

Although we have learned much about the features, onset, and course of BSDs, these disorders are prevalent, recurrent, and associated with significant impairment, and are not yet well understood. This article presented a reward hypersensitivity perspective on BSDs, its relevance for understanding the period of adolescence as an “age of risk” for these disorders, supporting evidence, and major unresolved issues that provide directions for future research. It also presented integrated reward-circadian and reward-immune models of BSDs that should provide even greater understanding of the mechanisms underlying these disorders and additional future research directions derived from these integrated models.

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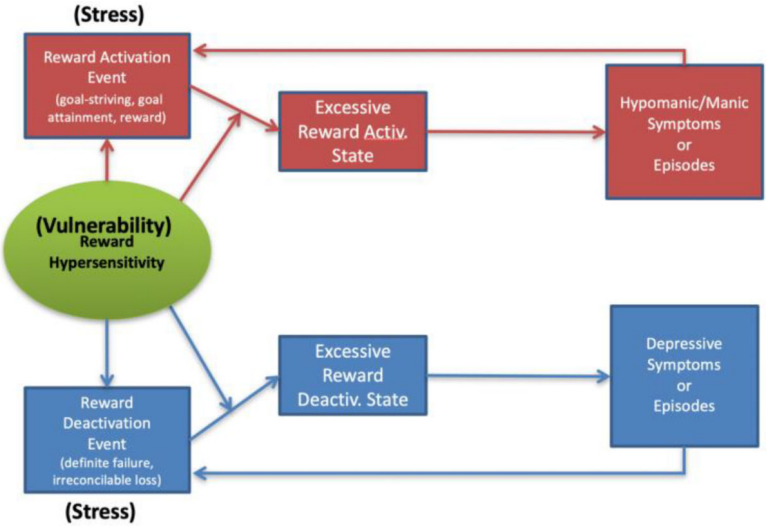


**Figure 1.**

Reward Hypersensitivity Model of Bipolar Specturm Disorders Adapted from Alloy, Nusslock, & Boland (2015). *Annual Review of Clinical Psychology, 11, 213–250.*

Note: The model is conceptual and not a path diagram.

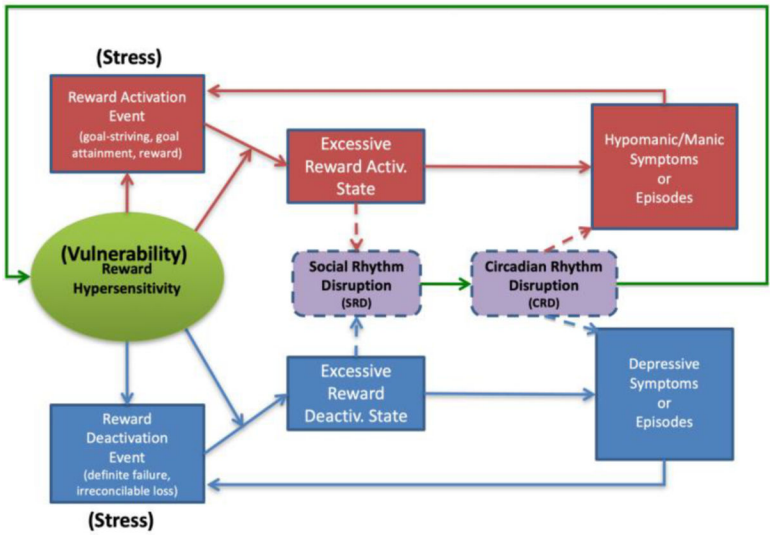


**Figure 2.**

Integrated Reward Circadian Rhythm (RCR) Model of Bipolar Specturm Disorders Adapted from Alloy, Nusslock, & Boland (2015). *Annual Review of Clinical Psychology, 11, 213–250.*

(Dashed lines indicate mediation)

Note: The model is conceptual and not a path diagram.

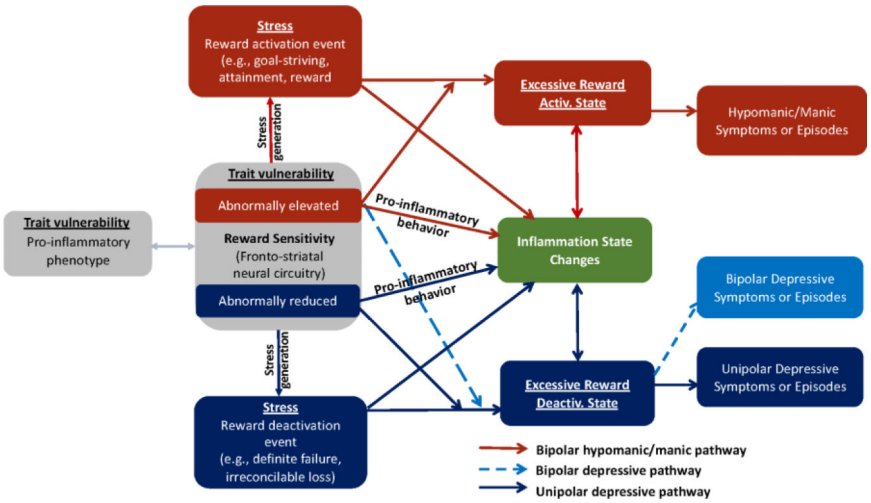


**Figure 3.**

Integrated Reward-Inflammation Model of Unipolar Depression and Bipolar Disorder Symptoms

Note: The model is conceptual and not a path diagram.