IMPULSIVITY AND SLEEP AND CIRCADIAN RHYTHM DISTURBANCE AS INTERACTIVE RISK FACTORS FOR BIPOLAR DISORDER MOOD SYMPTOM AND EPISODE ONSET: EVIDENCE FROM AN ECOLOGICAL MOMENTARY ASSESSMENT (EMA) STUDY

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ABSTRACT

Impulsivity and sleep and circadian rhythm disturbance are two core features of bipolar disorder that are elevated antecedents to bipolar disorder onset and persist even between mood episodes; their pervasive presence in bipolar disorder suggests that they may be particularly relevant to better understanding bipolar disorder etiology, onset, and course. Given considerable research demonstrating bidirectional associations between sleep and circadian rhythm disturbance and impulsivity in healthy individuals, it is surprising that little research has examined how these core features interact to impact bipolar disorder symptomatology, onset, and course. In a sample of late adolescents and young adults (N = 150) at low or high risk for developing bipolar disorder, we employed a naturalistic experiment in the context of an ecological momentary assessment (EMA) design to examine relationships between impulsivity, sleep and circadian rhythm alterations, and mood symptoms in everyday life. Furthermore, we sought to understand how the relationships between sleep and circadian rhythm alterations and mood fluctuation, collected during the EMA study, prospectively predicted mood symptom severity and mood episode onset at a 6-month follow-up. Linear regression, logistic regression, and multi-level modeling (MLM) revealed that higher impulsivity predicted increased mood symptoms during the EMA study, and less total sleep time (measured by actigraphy) predicted increased next-day EMA-assessed mood symptoms. Interaction analyses suggested that dim light melatonin onset time, total sleep time, and sleep onset latency moderated the relationship between impulsivity and mood symptoms (both next-day and at 6-month follow-up). Results are discussed in terms of their contribution to the existing literature. Findings highlight the necessity of multi-method, nuanced

examination of the dynamic relationships between impulsivity and sleep and circadian disturbance within bipolar disorder.

Keywords: Impulsivity, sleep disturbance, circadian rhythm disturbance, bipolar disorder, risk, mania, hypomania, depression

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CHAPTER 1

MANUSCRIPT IN JOURNAL ARTICLE FORMAT

Introduction

Bipolar disorder is a psychiatric illness that involves periods of extreme highs (mania or hypomania) and extreme lows (depression) occurring within the same individual. It is the sixth leading cause of disability worldwide and afflicts an estimated 60 million people (World Health Organization, 2006). Affected individuals exhibit multiple types of role-related and functional impairment, including impairment in work productivity and employment, social functioning, and health-related quality of life (Dean, Gerner, & Gerner, 2004; Merikangas et al., 2007). Although substantial functional impairment occurs during depressive and (hypo)manic episodes as a direct result of mood disturbance, this impairment persists even between episodes (Robinson et al., 2006a). Notably, deficits persist during euthymia in two particular domains: sleep and circadian rhythm disturbance and heightened impulsivity (Harvey, 2008; Ng et al., 2015; Robinson et al., 2006a; Swann, Anderson, Dougherty, & Moeller, 2001). Moreover, these two features are pervasive aspects of the illness. They appear across mood states and throughout the course of bipolar disorder, lending credence to the supposition that they are state-independent, core features of the disorder.

Growing evidence suggests that both heightened impulsivity and sleep and circadian rhythm disturbance precede first onset of bipolar disorder, signifying that these domains may be critical for bipolar etiology, onset, and course (Alloy et al., 2009; Ng et al., 2015, 2016). With respect to heightened impulsivity, evidence shows that self-reported trait impulsivity is elevated in individuals at genetic or behavioral high risk for developing bipolar disorder (Alloy et al., 2009; Chapman et al., 1984; Johnson, Carver, Mulé, & Joormann, 2013; Kwapil et al., 2000; Lombardo et al., 2012). However, it is important to note that impulsivity is a complex and multi-faceted construct that has been defined and measured in many different ways (Sharma, Markon, & Clark, 2014). Thus, different facets of self-reported impulsivity have been studied in relation to bipolar disorder. Barratt and colleagues (Barratt, 1959; Patton et al., 1995) found a three-factor structure for impulsivity that included attentional impulsiveness (the inability to concentrate or focus attention), motor impulsiveness (the tendency to act without thinking), and nonplanning impulsiveness (lack of future planning or foresight) (Bari et al., 2016). In one study, non-planning impulsiveness was elevated during the depressive phases of bipolar disorder, whereas motor impulsiveness was found to be elevated during the manic phases (Swann et al., 2008). Other factor structures for self-reported impulsivity have been proposed, including a five-factor structure by Whiteside and Lynam (2001), consisting of sensation seeking, lack of premeditation, lack of perseverance, positive urgency (the tendency to act rashly in the presence of positive emotion), and negative urgency (the tendency to act rashly in the presence of negative emotion). The latter two facets, positive and negative urgency, may be particularly relevant to bipolar disorder, given that mood dysregulation is the central component of the illness; periods of high and low mood may facilitate rash action, and rash action may, in turn, facilitate mood dysregulation.

In addition to self-reported impulsivity, measures of behavioral impulsivity and risk-taking behaviors have been studied in relation to bipolar disorder risk. Evidence for elevated behavioral impulsivity in participants at high risk for bipolar disorder is more mixed, although one meta-analysis (Bora, Yucel, & Pantelis, 2009) found that behavioral impulsivity deficits were present for relatives of bipolar disorder individuals. With regard to risk-taking behavior, in one study, the Balloon Analogue Risk Task, a laboratory behavioral task created to measure risk-taking behavior, was administered to participants with bipolar disorder and their first degree relatives. Compared to healthy controls, risk-taking behavior was elevated in both participants with bipolar disorder and their first degree relatives (Hıdıroğlu et al., 2013). Taken together, this evidence suggests that certain facets of impulsivity are not merely vestiges of mood disturbance, but instead represent antecedents and possible risk factors for developing the disorder.

Sleep and circadian rhythm disturbances also have been proposed as vulnerabilities for developing bipolar disorder (Lenox, Gould, & Manji, 2002; McClung, 2007). Substantial evidence clearly links abnormalities in sleep/wake cycles and circadian cycling to bipolar disorder and its course (Alloy, Ng, Titone, & Boland, 2017; Alloy, Nusslock, & Boland, 2015; Harvey, 2008; Ng et al., 2015). Moreover, efficacious treatments for bipolar disorder often involve deliberately phase shifting circadian rhythms, evidence that mood pathogenesis may be related to an alteration or abnormality in the sleep and/or circadian systems (Harvey, 2008). Although no truly prospective research demonstrates that circadian rhythm disturbance predicts first onset of bipolar disorder, several lines of evidence suggest that circadian rhythm dysregulation may have etiological significance for the illness.

First, intrinsic abnormalities in circadian regulation may confer vulnerability to mood dysregulation. Genetic studies suggest several genes that regulate circadian rhythm expression (most notably, the circadian locomotor output cycles kaput (CLOCK) gene and the GSK3-β gene) also are modestly associated with bipolar disorder (Benedetti et al., 2003; Daniel F Kripke, Nievergelt, Joo, Shekhtman, & Kelsoe, 2009; Shi et al., 2008). These genetic associations suggest that intrinsic circadian abnormalities may denote pre-existing vulnerability; altered circadian cycling has been posited as a potential bipolar disorder endophenotype (Lenox et al., 2002). Moreover, alterations to the timing of the melatonin hormone (onset of melatonin is an accurate physiological indicator of circadian phase in humans) have been shown in bipolar disorder (Kennedy, Kutcher, Ralevski, & Brown, 1996; Lewy et al., 1985). For individuals at risk for developing bipolar disorder, one study found that in comparison to healthy controls, light exposure suppressed melatonin more easily (Nurnberger et al., 1988). Overall, preliminary evidence from both genetic and melatonin studies suggests that intrinsic circadian rhythm abnormalities may precede bipolar disorder onset.

A second circadian-related risk factor for bipolar disorder may be difficulty with external entrainment of the circadian system in response to environmental change. Although the circadian system can operate independently of external input, it responds to outside entrainment by light, social cues, and feeding cues, among other variables (Duffy & Wright, 2005; Mistlberger & Skene, 2004). One related theory of mood disorder onset is the *social zeitgeber theory* (Ehlers, Frank, & Kupfer, 1988; Grandin, Alloy, & Abramson, 2006), which posits that disruption in social rhythms (e.g., wake and sleep times, meal times, and social contact) can trigger circadian rhythm disruption, which can cause physiological changes leading to mood disturbance. Although several parts of this theory have never been empirically tested, preliminary evidence demonstrates that individuals at high risk for developing bipolar disorder have more irregular social rhythms (Bullock, Judd, & Murray, 2011; Meyer & Maier, 2006; Shen, Alloy, Abramson, & Sylvia, 2008), and one study found that low social rhythm regularity prospectively predicted the first onset of a bipolar spectrum disorder (Alloy, Boland, Ng, Whitehouse, & Abramson, 2015). Thus, poor external entrainment of the circadian system in response to external social stressors also might serve as a risk factor for developing bipolar disorder.

A final circadian-related risk factor for bipolar disorder is chronotype, the inter-individual variation in preference for wake time, sleep time, and completion of activities during the day. Depressive and euthymic phases of bipolar disorder have been associated with evening chronotype (i.e., preference for going to bed later, waking later, and doing strenuous activity in the late afternoon or evening) (Melo et al., 2017). Although chronotype is understood to be a stable, trait-like dimension, and thus, might be considered a pre-existing risk factor for bipolar disorder, studies examining the relationship between bipolar disorder risk and evening chronotype are mixed (Melo et al., 2016). However, given the relative stability of chronotype throughout the lifetime (Adan et al., 2012), it is an intriguing possible circadian-related risk factor for developing bipolar disorder.

Sleep disturbance, although closely intertwined with circadian rhythm disturbance, has different neurological substrates, and thus, may have a different relationship with bipolar disorder course and etiology (Harvey, 2008). Although sleep disturbance represents a clear prodrome for mania episode onset (Jackson, Cavanagh, & Scott, 2003), evidence for disturbed sleep preceding bipolar disorder onset in high-risk samples is inconclusive (see Ng et al., 2015). However, there is evidence that subjective, self-reported measures of sleep disturbance are elevated in bipolar disorder high risk samples (Jones, Tai, Evershed, Knowles, & Bentall, 2006; Ritter et al., 2012), whereas evidence for objectively measured sleep disturbance (i.e., actigraphy, polysomnography) is more mixed (Ankers & Jones, 2009; Ritter et al., 2012). Thus, despite mixed findings, sleep disturbance is a prodrome to manic episodes and remains an intriguing possible risk factor for bipolar disorder.

Impulsivity, circadian rhythm disturbance, and sleep disturbance represent core features of bipolar disorder, and preliminary evidence suggests that they may confer vulnerability for developing the disorder. However, few truly prospective studies have examined these features as possible interactive risk factors for mood episodes. Given the large body of evidence demonstrating bidirectional influences between impulsivity and sleep and circadian rhythm disturbance in healthy controls (Caci et al., 2005; Caci, Robert, & Boyer, 2004; Goel, Rao, Durmer, & Dinges, 2009; Lowe, Safati, & Hall, 2017), it is surprising that so few studies have examined their interaction in the context of bipolar disorder risk, onset, and course.

The Current Study

This study investigated impulsivity and sleep and circadian rhythm disturbance as potential interactive risk factors for developing mood symptoms and episodes by employing a naturalistic, ecological momentary assessment (EMA) design. Furthermore, it used a variety of measures (e.g., physiological, self-report, diary, actigraphy) to examine the relationship of a naturalistic social rhythm disruption to sleep and circadian parameters and prospective onset of mood disorder symptoms or episodes.

Emerging adulthood and the transition to college are high-risk periods for development of a first mood disorder episode (Compas & Phares, 1991; Compas, Wagner, Slavin, & Vannatta, 1986). Moreover, college is a time when many students have highly irregular schedules and experience heightened sleep disturbance due to multiple factors such as variable course schedules and increased engagement in evening social activities (Buboltz, Brown, & Soper, 2001). Thus, the current study employed a sample of university students and measured sleep, circadian, and mood parameters surrounding a naturalistic environmental stressor and disruption of social rhythms idiographic to each participant (e.g., studying for and taking a final exam, researching a final paper). Additionally, these participants were followed prospectively to assess mood symptoms and depression or (hypo)manic episode onset; sleep and circadian parameters from the EMA study were used to prospectively predict mood symptoms/episodes.

Study Hypotheses

Hypothesis 1. Given evidence that self-reported and behavioral measures of impulsivity are not highly correlated, and that both types of measures separately predict the occurrence of real-life impulsive behaviors (Sharma et al., 2014), we tested both self-reported impulsivity (measured by the UPPS-P and Barratt Impulsivity scale, described below) and behavioral impulsivity (measured by the Balloon Analogue Risk Task (BART), described below) as predictors of average (hypo)manic and depressive mood symptoms. We hypothesized that self-reported negative urgency (UPPS-P), self-reported non-planning impulsivity (i.e., lack of future planning or foresight as measured by the Barratt Impulsivity Scale), and self-reported Barratt total score would predict depressive symptoms during the EMA study, whereas self-reported positive urgency (UPPS-P score), self-reported Barratt total impulsivity score, and risk-taking behavior (BART score) would predict (hypo)manic symptoms.

Hypothesis 2. We also predicted that sleep (decreased total sleep time and increased sleep onset latency as measured by actigraphy) and circadian rhythms (later skin temperature acrophase and later melatonin onset time) would predict increased next-day depressive and (hypo)manic symptoms during the EMA study.

Hypothesis 3. We further predicted that the relationship between sleep and circadian rhythm disturbance (e.g., later skin temperature acrophase, later melatonin onset time, decreased total sleep time, or increased sleep onset latency) and increased next-day mood symptoms (daily average of depressive and hypomanic symptoms) would be stronger among participants with high self-reported and behavioral impulsivity (UPPS-P negative urgency, UPPS-P positive urgency, Barratt Non-planning Impulsivity score, Barratt Total Score, and Balloon Analogue Risk Task (BART) score).

Hypothesis 4. Finally, we predicted that specific facets of self-reported/ behavioral impulsivity (as specified in Hypothesis 1) and specific facets of sleep and circadian rhythm disruption (as specified in Hypothesis 2) would interact to predict higher likelihood of developing a mood episode (measured by presence of mood episode determined by SADS-C ratings) and more severe prospective mood symptoms (measured by BDI and ASRM scores). Specifically, we tested changes in sleep and circadian rhythm measures (i.e., differences between sleep and circadian parameters in the disruption phase compared to the baseline phase of EMA study) in interaction with self-reported/behavioral impulsivity as a predictor of mood disorder course (episode presence and mood symptom severity).

Method

Recruitment and Participants

Participants were a subset of adolescents and young adults (aged 14 - 21) who were recruited in a two-phase screening process from 13 local high schools in the Philadelphia area and Temple University for Project TEAM (the Teen Emotion and Motivation Study), a multi-wave prospective study that examined vulnerability to bipolar spectrum disorders (for full study details, see Alloy et al., 2012). Participants were screened in two waves starting in 2008. Across both waves, 9,991 14-19 year-old adolescents were screened with two self-report questionnaires measuring reward sensitivity, the Behavioral Activation Scale (BAS) of the Behavioral Inhibition System/Behavioral Activation System Scales (BIS/BAS; Carver & White, 1994) and the Sensitivity to Reward (SR) subscale of the Sensitivity to Punishment Sensitivity to Reward Questionnaire (SPSRQ; Torrubia, Ávila, Moltó, & Caseras, 2001). One group of eligible participants, considered to be at low risk for developing a bipolar disorder, scored in the 40^{th}-60^{th} percentile on both the BAS and SR; this was the moderate reward sensitivity (MRew) group. The other group of eligible participants, considered to be at high risk for developing a bipolar disorder, the high reward sensitivity (HRew) group, scored in the 85^{th}-99^{th} percentile on both reward sensitivity questionnaires. In Phase II, participants completed an expanded Schedule for Affective Disorders and Schizophrenia – Lifetime (exp-SADS-L) diagnostic interview given by interviewers blind to participants' risk group or symptom status (Alloy et al., 2008; 2012; Endicott & Spitzer, 1978). Participants were excluded from the final TEAM sample if they had: 1) a prior history of *DSM-IV* or RDC bipolar spectrum disorder diagnosis (i.e., bipolar I disorder, bipolar II disorder, cyclothymia, or bipolar disorder not otherwise specified); 2) a hypomanic episode occurring prior to the date of Phase I screening; 3) a diagnosis of any *DSM-IV* or RDC psychotic disorder or current psychotic symptoms; 4) poor English speaking/writing ability; or 5) a serious medical illness that prevented participation.

The participants in our final sample (N = 150) were recruited from those who already had been participating in the larger longitudinal Project TEAM study. These participants were contacted by phone or in-person during one of their regularly scheduled prospective assessments for Project TEAM, and asked to participate in an ecological momentary assessment (EMA) study of mood, social rhythms, reward sensitivity, and goal striving. They were informed that the study would last 20 days, and would involve a period of personal goal striving (typically taking the form of studying for and completing final exams, or researching and writing a final paper). If they agreed, the EMA study occurred between regular prospective follow-up assessments in the overall study.

The final sample (N = 150) was 59% female, 56% white, and aged 18-27 years (M = 21.86 years, SD = 2.11) at the time of the EMA study. See Table 1 for a full overview of demographic characteristics of the sample and number of usable observations for each type of data collected during the EMA study. Thirty-one participants (20.6%) reported taking medication (OTC, prescribed, etc.), and of those, 6 participants reported taking medication that might affect sleep (4.0%), whereas 24 participants reported taking medication that might affect mood (16%). However, only two participants reported taking prescribed psychotropic medication (1.3%).

Procedure

Participants in the final EMA sample completed measures at four distinct timepoints: screening, TEAM Project baseline, EMA study, and longitudinal follow-up. During the initial screening, participants completed the BAS and SR measures of reward sensitivity. During the TEAM Project baseline, participants completed the exp-SADS-L diagnostic interview to ascertain baseline psychiatric diagnosis, a self-report measure of chronotype, two self-report measures of trait impulsivity, and a behavioral measure of risk-taking behavior. During the EMA study timepoint, participants completed symptom and affect ratings, and measures of sleep via actigraphy, self-report, skin temperature, melatonin onset time, and social rhythm regularity. Finally, at the longitudinal follow-up timepoint (occurring 3-12 months after the EMA study), participants completed a follow-up exp-SADS-Change diagnostic interview and mood symptom self-report measures. See Figure 1 for a visual depiction of measures administered at each timepoint.

For the EMA portion of the study, participants were invited to the laboratory, where they completed a separate written informed consent for the EMA study and were briefed thoroughly with a 1-hour instructional session on study procedures. The study protocol was reviewed and approved by Temple University's Institutional Review Board. Participants were informed that the study would take 20 consecutive days: 5 days of a "baseline" period, 10 days when they were studying for and taking a final exam (or participating in another goal-striving event), and 5 days of an "outcome" period, when they had finished goal-striving and most likely learned the outcome of their goal-striving. During the instructional session, it was emphasized that participants should go about their daily lives as usual. They also were instructed on completing nightly EMA questionnaires (e.g., sleep diary), wearing an Actiwatch (to measure sleep/wake parameters) and Thermochron iButtons (to measure skin temperature), and responding to three EMA text messages per day on their cell phones. Participants practiced answering text messages and responding in the lab. Participants also received materials and instructions for completing the dim light melatonin onset (DLMO) procedure 3 times: on the first evening of the EMA study (day 1), on the evening of day 10, and on the last evening of the EMA study (day 20). Participants returned to the lab three times following the instructional session to drop off saliva samples collected during the DLMO procedure after Days 1, 10, and 20. At the post-Day 20 drop-off session, participants turned in all equipment (light-attenuating goggles, DLMO kits, Actiwatches, and iButtons), and they completed the clinician administered Life Events Interview. They also completed a goal-striving outcome questionnaire.

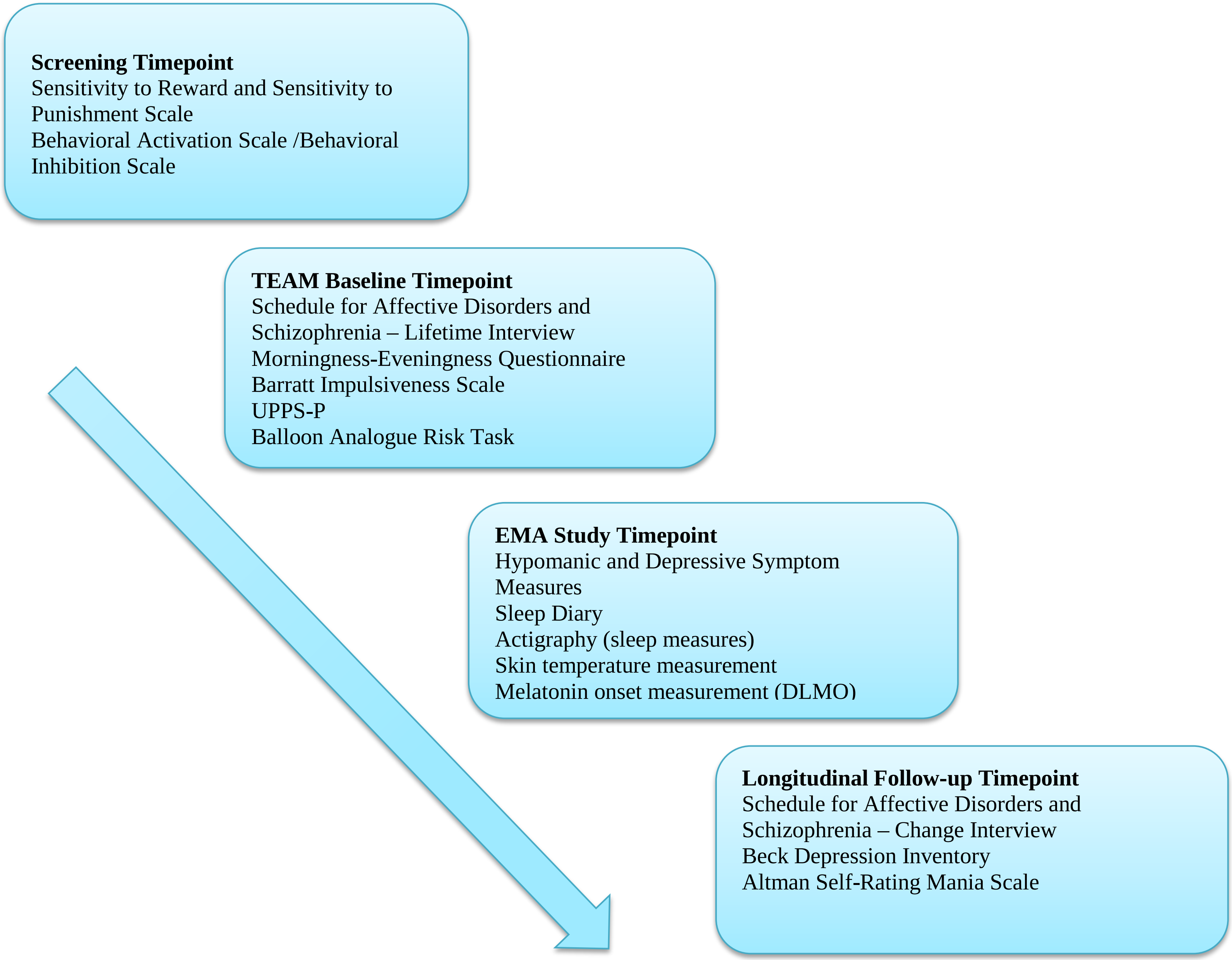


Figure 1. *Four distinct timepoints and corresponding measures administered at each timepoint*

Measures

Screening Measures

Behavioral Inhibition Scale/Behavioral Activation Scale (BIS/BAS). The BIS/BAS Scales were developed to measure the personality/trait variables of behavioral activation (sensitivity to reward) and behavioral inhibition (sensitivity to punishment) (Carver & White, 1994). For identifying participants at low and high risk for BSD, we used the total score on the Behavioral Activation Scale (BAS), which contains three subscales: Fun-Seeking, Drive, and Reward Responsiveness. The BIS/BAS has shown internal consistency and test-retest reliability (Carver & White, 1994). In the Phase I screening sample of the TEAM Project, the BAS total score showed high internal consistency (α = .80) (Alloy et al., 2012). The BIS/BAS also has demonstrated good construct validity (Colder & O'Connor, 2004; Harmon-Jones & Allen, 1997).

Sensitivity to Punishment Sensitivity to Reward Questionnaire (SPSRQ). This scale was developed by Torrubia and colleagues (2001) to measure the constructs of sensitivity to reward and sensitivity to punishment as detailed by Gray's personality model (1994). It consists of 48 "yes" or "no" questions. The Sensitivity to Reward Scale (SR) differs from the BAS in that it attempts to measure sensitivity to specific rewards (e.g. money, sex, social power, approval, and praise), whereas the BAS attempts to measure sensitivity to reward as a general concept. The SR scale shows good internal reliability and construct validity (Torrubia et al., 2001). The SR scale's internal consistency in the TEAM Phase I screening sample was α = .76, and the BAS total and SR scales correlated r = .40 with each other (Alloy et al., 2012).

Baseline Measures

Psychiatric diagnoses. To ascertain baseline mood disorder diagnosis, we administered an expanded version of the Schedule for Affective Disorders and Schizophrenia – Lifetime interview [exp-SADS-L, (Alloy et al., 2008; 2012; Endicott and Spitzer, 1978)] expanded to allow *DSM-IV-TR* diagnoses as well as Research Diagnostic Criteria [RDC; (R. L. Spitzer, Endicott, & Robins, 1978)] diagnoses. This semi-structured interview assesses past and current Axis I *DSM-IV-TR* and RDC disorders. The exp-SADS-L includes additional clarifying items added to the depression/mania sections, use of five point scales to rate severity, and the addition of modules for eating disorders, attention deficit/hyperactivity disorder, and acute stress disorder. The exp-SADS-L has demonstrated high inter-rater reliability ($\kappa > .96$ for diagnosing bipolar spectrum disorders) based on 105 jointly rated interviews (Alloy et al., 2008). Participants who were diagnosed with a bipolar spectrum disorder or who experienced a hypomanic episode prior to TEAM Phase I screening were excluded from our final sample.

Morningness-Eveningness (chronotype or circadian preference). Participants completed the 19-item Morningness-Eveningness Questionnaire (MEQ; Horne & Ostberg, 1976) to assess chronotype or circadian preference. This dimension represents a trait-like individual preference for certain wake-times, bedtimes, and peak activity times. Individuals who endorse high eveningness prefer later bedtimes, later wake-times, and prefer to complete activities during the evening as opposed to the morning (Adan et al., 2012). The MEQ has been shown to be a reliable measure across samples in several countries, with reliability coefficients ranging between .78 and .86 (Adan & Natale, 2002; Chelminski, Ferraro, Petros, & Plaud, 1997; Neubauer, 1992). Across a three-month period, the MEQ also demonstrates strong test-retest reliability (r = .88–.89) (Larsen, 1985; Neubauer, 1992). Several other studies have shown that the MEQ score has strong construct validity, as eveningness scores are associated with later circadian phase as measured by minimum body temperature time (Baehr, Revelle, & Eastman, 2000; Duffy, Dijk, Hall, & Czeisler, 1999) in addition to later melatonin onset times (Benloucif et al., 2005). In our sample, test-retest reliability is also strong (r = .65–.92). Internal consistency of the MEQ in our sample was $\alpha = .85$. Higher MEQ scores reflect greater morningness.

Trait impulsivity. Participants completed the Barratt Impulsiveness Scale (BIS-11) (Patton, Stanford, & Barratt, 1995), a 30-item self-report measure designed to assess the personality/behavioral construct of impulsivity. The BIS is arguably the most commonly used self-report measure for assessment of trait impulsiveness; it has very strong test-retest reliability and validity (Stanford et al., 2009). Participants also completed the UPPS-P (Urgency, Premeditation, Perseverance, Sensation Seeking, and Positive Urgency) Impulsive Behavior Scale, a 59-item self-report measure designed to assess five different factors of trait impulsivity, which has been validated against measures of risky behaviors and shows good predictive validity (Cyders et al., 2007; Whiteside, Lynam, Miller, & Reynolds, 2005). Internal consistency of the BIS-11 and UPPS-P in our sample was .80 and .92, respectively, and higher scores on both reflect greater impulsivity.

Risk-taking behavior. At baseline of the TEAM study, participants completed the Balloon Analogue Risk Task (BART), a computerized measure of risk-taking behavior (Lejuez et al., 2002). We used the adjusted average number of pumps as a measure of laboratory risk-taking behavior; a higher number reflects higher impulsivity. The BART has demonstrated reasonable test-retest reliability (White, Lejuez, & de Wit, 2008) and shows strong associations with "real-world" risk-taking behaviors in clinical and non-clinical samples (Aklin, Lejuez, Zvolensky, Kahler, & Gwadz, 2005; Fernie, Cole, Goudie, & Field, 2010).

EMA Measures

EMA data were collected for 20 days at varying intervals; DLMO was measured at three timepoints (Day 1, Day 10, and Day 20), whereas other variables were collected once a day, three times a day, or continuously.

Hypomanic and depressive symptoms. Participants rated their mood symptoms three times per day (morning, afternoon, and evening). They rated four hypomania symptoms (happy, self-confident, needing less sleep, talkative) and four depression symptoms (sad, hopeless, low self-esteem, low energy) on a scale of 0 to 4, 0 = not at all, 2 = moderately, and 4 = extremely, on how much they felt each symptom right now. These symptoms were taken from two self-report measures: the Altman Self-Rating Mania scale (Altman, Hedeker, Peterson, & Davis, 1997) and the Beck Depression Inventory-II (Beck, Steer, & Brown, 1996).

Negative and positive affect ratings. In conjunction with the symptom ratings, participants also rated their affect three times per day (morning, afternoon, and evening). They rated four negative affect (upset, guilty, hostile, scared) and four positive affect items (excited, interested, determined, active) "on a scale of 0 to 4, 0 = not at all, 2 = moderately, and 4 = extremely, how much they felt each affect right now. These symptoms were taken from the Positive and Negative Affect Scales (Watson, Clark, & Tellegen, 1988).

Sleep/wake disturbance and activity parameters. Philips Actiwatches provide a non-invasive measurement of sleep/wake cycles with the added benefit of minimally disrupting daily routines. Actigraphy also has high correlations with polysomnography and sleep diaries (Kushida et al., 2001). Participants wore an Actiwatch on the non-dominant wrist for 20 continuous days. They were instructed to remove the Actiwatch only when it might get wet (e.g., in the shower). Following standard procedures, two main variables were calculated from the actigraphy data: sleep onset latency (time to fall asleep) and sleep duration.

Participants also filled out a nightly online sleep diary to assess parameters such as bedtime, wake time, how long it took to fall asleep, sleep quality, naps, caffeine, medication use, and duration of removal of Actiwatch or iButtons. These responses were used to calculate self-reported sleep parameters (e.g., total sleep time and sleep onset latency).

Skin temperature. Skin temperature was measured continuously via Thermocron iButtons, a non-invasive, ambulatory wireless system for monitoring skin temperature. Distal skin temperature is inversely correlated and slightly phase advanced with core body temperature, and core body temperature is a reliable marker of circadian phase (Hasselberg, McMahon, & Parker, 2013; Sarabia, Rol, Mendiola, & Madrid, 2008). An iButton was placed on the dominant wrist and secured with Velcro attached to a cotton sports wristband. Participants also wore a second iButton secured on a lanyard around the neck and above the outer layer of clothing; this served to measure the ambient (environmental) temperature. The iButtons continuously recorded data in 10-minute intervals. Cosinor analysis (Cornelissen, 2014) was used to characterize the skin temperature rhythms. Three variables of interest were derived from the skin temperature measurement: acrophase, amplitude, and mesor. However, only acrophase was used in this study. Acrophase, a measure of the skin temperature maximum, was used as a marker of circadian phase. Acrophase was measured in units of time subtracted from a baseline time; we calculated the time of the maximum value of the cosine fitted skin temperature curve relative to the local 0:00h. A higher acrophase value indicates a later circadian peak.

Melatonin onset time. Participants completed the Dim Light Melatonin Onset (DLMO) procedure on the evenings of Day 1, Day 10, and Day 20 of the study. Participants provided 10 saliva samples at 30-minute intervals at home while wearing light-attenuating goggles (Noir Medical Technologies, South Lyon, MI). They started the procedure five hours before their planned bedtime. Participants were instructed not to ingest food and to limit water intake to the 5 min. following each saliva sample during the procedure. Saliva (1.0ml – 3.0ml) was deposited into Salivette tubes containing absorbent polyester swabs; participants placed the swabs in their mouths for five minutes. Salivettes were refrigerated immediately and collected the next day for continued storage at -20 ^{o}C in the lab pending assay. Melatonin was assayed with ELISA in a laboratory at the University of Pennsylvania. The DLMO, a gold-standard marker of circadian phase (Goel, 2005, 2006), was defined as the first interpolated point at 3.0 pg/ml on the rising curve of melatonin concentration. Melatonin onset time was operationalized as minutes elapsed to melatonin onset from a standardized baseline time (local 0:00h). Later melatonin onset time reflects a later circadian phase.

Prospective Follow-up Measures

*Psychiatric diagnoses***.** To ascertain mood disorder episode diagnosis at a 3–12 month prospective follow-up timepoint, we administered an expanded Schedule for Affective Disorders and Schizophrenia – Change interview (exp-SADS-C; Alloy et al., 2008; Spitzer & Endicott, 1978) expanded to allow *DSM-IV-TR* diagnoses as well as RDC diagnoses. The exp-SADS-C measures the duration, timing, and severity of symptoms for various *DSM-IV-TR* and RDC mood, anxiety, psychotic, and substance use disorders since the last interview. Inter-rater reliability for the SADS-C is strong (kappa = 0.80) (Francis-Raniere, Alloy, & Abramson, 2006).

Depressive symptoms. The Beck Depression Inventory – II (BDI-II) (Beck et al., 1979; Beck, Steer, & Brown, 1996) was also administered at the follow-up session. This is a 21-item self-report questionnaire that measures severity of cognitive, affective, somatic, and motivational symptoms of depression. The test-rest reliability, internal reliability, and validity of this measure are excellent (Beck, Steer, & Garbin, 1988; Dozois, Dobson, & Ahnberg, 1998). The Internal State Scale (ISS) (Bauer, 1991; Bauer, Vojta, Kinosian, Altshuler, & Glick, 2000), a questionnaire developed to measure manic and depressive states in bipolar disorder, also was administered. The ISS consists of four empirically derived subscales, one of which is the Depression Index. The ISS possesses good internal consistency and convergent validity (Bauer, 1991). In our sample, the internal consistency of the ISS Depression subscale was $\alpha = .72$.

Hypomanic symptoms. Similarly, the Altman Self Rating Mania Scale (ASRM) (Altman et al., 1997) was given at the follow-up session. This is a 5-item self-report questionnaire that measures severity of five mania symptoms using a 5-point Likert scale.

The ASRM is highly correlated with other self-report measures of mania and with clinical interviews, demonstrating good convergent validity (Altman et al., 2001). Mania symptoms also were measured at follow-up using the Activation subscale of the ISS (described above). Internal consistency of the ISS activation subscale in our sample was $\alpha = .81$.

Data Analytic Plan

This study investigated relationships between sleep and circadian rhythm disruption, impulsivity, and mood symptoms/episodes, as collected during the course of a 20-day EMA study, followed by a prospective 3-12-month follow-up. Given measurements occurring over time, nested within individuals, the use of multilevel modeling (MLM) was appropriate. This design allowed for sensitive tests of the association between sleep and circadian rhythm parameters and mood symptoms in order to provide a more accurate, powerful examination of these real-time occurrences within individuals. MLM maximizes data usage because it is able to flexibly handle missing data. Analyses were conducted using the Mplus software package.

For Hypothesis 1, we used static, baseline measures of self-reported and behavioral impulsivity (Level-2, between-person variables) to predict to averages of (hypo)manic and depressive symptoms during the EMA study. For all multi-level modeling analyses (Hypotheses 2 and 3), we isolated the variability in the Level-1 predictors (e.g., sleep and circadian parameters predicting next-day symptoms) by person-mean centering the sleep and circadian rhythm parameters and including an aggregated 20-day person-level variable on Level 2 of the model. We also led sleep and circadian rhythm parameters by one day (n-1) in order to examine their effect on next-day mood symptoms. Additionally, we tested all multilevel models for random slopes, allowing slopes for the sleep and circadian relationship with mood symptoms to vary randomly between Level-2 units (individuals). We compared these models to random intercept models, and no significant differences were found between random slope and random intercept models; thus, random intercept models without random slopes are reported below.

Finally, for Hypothesis 4, to operationalize sleep and circadian rhythm change in response to an external social rhythm disruption, we calculated change scores between sleep and circadian rhythm parameters in the "disruption" phase (Days 6–15) and the "baseline" phase of the study (Days 1–5). We used the change scores as a measure of both direction and magnitude of change between "baseline" and "disruption" phases. These change scores and the baseline impulsivity measures were used to predict follow-up mood symptoms and episode onsets.

For all analyses to test Hypotheses 1 – 4, we controlled for reward sensitivity status, sex, and baseline depressive and (hypo)manic symptoms. In addition, for analyses testing Hypotheses 1, 3, and 4 involving baseline measures of impulsivity, we also controlled for the number of days between baseline and start of the EMA study. For analyses testing Hypothesis 4, we controlled for number of days between the end of the EMA study and the follow-up timepoint.

For all analyses that utilized symptom severity as the dependent variable, depressive and hypomanic symptoms were the main outcomes of interest. For EMA analyses, negative and positive affect also were used as outcome variables in the Exploratory Results section to examine replicability of the mood symptom findings. For longitudinal follow-up analyses, BDI and ASRM scores were the main dependent variables, but ISS-D and ISS-A scores also were used as outcomes in the Exploratory Results section to examine replicability of the findings.

Results

Preliminary Analyses

The means, standard deviations, and bivariate correlations between variables of interest are presented in Table 2. Bivariate correlational analyses were conducted between demographic and clinical variables (sex, age at start of EMA study, race, reward sensitivity status, and bipolar disorder diagnosis status) and the dependent variables in our main analyses (mood symptoms and affect during the EMA study; mood symptoms and episodes at the follow-up timepoint after the EMA study). The majority of demographic variables were not significantly correlated systematically with the dependent variables, but sex and reward sensitivity status showed significant correlations. Thus, we controlled for both sex and reward sensitivity status in all subsequent analyses.

The analyses for Hypothesis 4 used longitudinal follow-up data at the timepoint after the EMA study (*M* number of months between EMA study and diagnostic follow-up = 7.23). Semi-structured diagnostic interviews administered at this timepoint assessed prospective mood disorder diagnoses. Fifteen participants were diagnosed with a *DSM-IV-TR* or RDC major depressive episode, 20 were diagnosed with any type of depressive episode (major or minor), and 6 were diagnosed with a manic or hypomanic episode. Given the relative scarcity of mood episodes, the logistic regression analyses (described below) were underpowered, and the likelihood of detecting an effect for mood episodes was low.

Distributional assumptions were tested for the dependent variables in all analyses. Examination of residual plots revealed significant heteroscedasticity in the residuals of depressive symptoms and negative affect during the EMA study and BDI and ISS-D score at first follow-up after the EMA study. Several transformations were tested, and log(10) transformation of these variables resulted in more normal homoscedasticity of residuals. Therefore, log transformed versions of the variables listed above were utilized in all subsequent analyses.

Missing data proportions and patterns were examined for all variables of interest. For variables with less than 5% missing data, no further tests were run (Dong & Peng, 2013). For variables with more than 5% missing data, patterns of missing data were examined using t-tests, visual inspection of missing data patterns, and Little's Missing Completely at Random (MCAR) test (Little, 1988). MCAR was supported for all variables except for the Balloon Analogue Risk Task (BART) variable; follow-up symptom scores (e.g. BDI score, ASRM score) were higher for participants missing the BART score than not. Given that dependent variables met distributional assumptions and that the MCAR assumption was supported for almost all variables, the analyses were run in the MPlus statistical program with and without implementing Full Information Maximum Likelihood (FIML), a method of estimating missing data that allows for all available data to be used. Below, we report all analyses that consistently were significant using both listwise deletion and FIML. For results that were of incongruent significance when run with and without FIML, we chose to report the analyses without FIML, given that the BART did not meet the MCAR assumption.

Table 1. *Descriptive statistics for the participants who completed the EMA study*

TEAM Participant Characteristics	Mean (SD) or N (%)
N = 150	
Age, TEAM Time 1	18.40 (1.32)
Race (White)	84 (56.0%)
Gender (Female)	88 (58.7%)
Days between Time 1 and EMA	895.88 (901.52)
MDE History (Time 1)	60 (40.0%)
(Hypo)mania History (Time 1)	23 (15.3%)
BSD Diagnosis during TEAM	43 (28.7%)
Reward Sensitivity Status (High)	107 (71.3%)
EMA Study Characteristics	
Age, Start of EMA Study	21.86 (2.11)
Days between EMA and Follow-up	217.02 (227.14)
Bedtime Survey (N Observations)	2447 (81.6%)
Daytime Survey (N Observations)	2876 (95.9%)
Actigraphy (N Observations)	2183 (72.7%)
iButton Skin Temp. (N Observations)	1444 (48.1%)
DLMO (N Observations)	2125 (70.8%)
Overall % Usable Observations	73.8%

Note. TEAM = Team Emotion and Motivation Study; MDE = Major Depressive Episode; DLMO = Dim Light Melatonin Onset. Means are presented with standard deviations in parentheses, if applicable.

Table 2. *Summary of variable means, standard deviations, and bivariate correlations*

Measure	**Mean**	**SD**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
1. Depressive Symptoms	1.31	0.26	–.14	.74±	–.03	.29±	.23±	.19*	.27±	–.06	.12	.09	–.004	–.03	–.17	.03	.42±	.10	.58±	.19*	.35±	.36±	–.09
2. Hypomanic Symptoms	2.09	0.49	–	.04	.87±	–.05	.16	–.07	.09	.01	.09	–.08	–.28±	–.04	.22*	.25*	–.15	.34±	–.02	.32±	–.13	.18	.15
3. Negative Affect	1.28	0.28		–	.13	.30±	.26±	.13	.20*	–.09	.19*	.06	–.06	–.04	.01	.15	.26±	.19*	.55±	.19*	.25±	.36±	.006
4. Positive Affect	2.28	0.58			–	.04	.31*	–.11	.10	–.01	.12	–.11	–.29±	–.01	.27*	.23*	–.13	.37±	–.01	.33±	–.10	.21*	.20*
5. UPPS-P Negative Urgency	28.21	8.07				–	.70±	.32±	.46±	.07	.07	.04	–.05	.11	–.04	.10	.25±	.06	.33±	.23*	.27±	.34±	–.14
6. UPPS-P Positive Urgency	29.22	9.51					–	.24±	.46±	.05	.05	.13	.02	.08	.07	.19	.24*	.21*	.30±	.35±	.24±	.43±	–.19*
7. Barratt Non-Planning Impul.	21.33	4.28						–	.74±	–.12	.09	.09	.03	.13	–.06	–.04	.30±	–.01	.26±	.03	.21±	.28±	–.29*
8. Barratt Total	65.80	10.75							–	–.05	.06	.17	–.06	.10	–.02	–.02	.32±	.06	.25±	.20*	.17	.36±	–.20*
9. Balloon Analogue Risk Task	35.89	13.70								–	.05	–.06	–.09	–.18	–.10	–.04	–.09	.03	.14	.11	.02	.17	.08
10. Total Sleep Time (SR)^	7.37	1.98									–	.45±	.04	–.001	–.10	–.27*	.10	.09	.08	.04	.01	.03	.12
11. Total Sleep Time (Act.)^	6.90	1.99										–	.23*	.33±	.19	–.15	.09	–.01	.01	.16	.07	.05	.03
12. Sleep Onset Latency (SR)	33.88	52.00											–	.27±	.29±	–.02	.10	–.002	–.001	–.13	–.04	–.14	–.20*
13. Sleep Onset Latency (Act.)	13.88	20.94												–	.25*	.04	–.12	–.07	–.02	.004	–.01	–.16	–.16
14. Skin Temp. Acro.	-1.58	222.83													–	.33±	–.27*	.07	–.006	.08	–.20	.02	–.20
15. DL Melatonin Onset Time^	21:56	1.50														–	–.002	.25*	.02	.23	.04	.24*	–.36±
16. Time 1 BDI	8.73	8.37															–	–.04	.41±	.16	.49±	.30±	–.09
17. Time 1 ASRM	5.86	3.76																–	.07	.26*	.02	.15	–.12
18. BDI (First Follow-up)	4.50	5.43																	–	.15	.51±	.38±	–.10
19. ASRM (First Follow-up)	3.79	3.77																		–	.16	.47±	–.05
20. ISS-D (First Follow-up)	3.07	1.48																			–	.46±	–.12
21. ISS-A (First Follow-up)	10.54	4.39																				–	–.13
22. Morningness-Eveningness	44.88	8.83																					–

Note. ^ Total Sleep Time (SR and Act.) is reported in hours. Sleep Onset Latency (SR and Act.) is reported in minutes. DL Melatonin Onset Time is reported as a clock hour. Skin Temp. Acro. is reported in minutes centered around the median value. SR = Self-report; Act.= Actigraphy-measured; Acro. = Acrophase; DL = Dim Light ; BDI = Beck Depression Inventory; ASRM = Altman Self-Rating Mania Scale; ISS-D = ISS Depression subscale score; ISS-A = ISS Activation subscale score; Morningness-Eveningness = Morningness Eveningness Questionnaire

* $p < .05$

± $p < .01$

Hypothesis 1

Linear regressions examined the relationship between Time 1 impulsivity measures (BART, Barratt Non-planning Impulsivity subscale score, Barratt Total score, UPPS-P Negative Urgency and Positive Urgency) and 20-day averages of (hypo)manic and depressive symptoms during the EMA study. All analyses controlled for sex, reward sensitivity status, baseline mood symptoms (as measured by the BDI or ASRM at Time 1) and number of days between Time 1 and the start of the EMA study. All planned analyses for Hypothesis 1 were non-significant (see Table 3 for detailed results). Exploratory analyses were run using additional measures of impulsivity as predictors and EMA positive/negative affect ratings as outcomes. See the Exploratory Analyses in Chapter 2 for full results.

Table 3. *Results of linear regressions (baseline impulsivity measures predicting depressive and hypomanic symptoms from Hypothesis 1*

Measure	Depressive symptoms (z)		Hypomanic symptoms (z)	
Between-Person	Coefficient	*p*	Coefficient	*p*
BART[1] Score	--	--	-0.04	0.69
UPPS-P Positive Urgency	--	--	1.28	0.20
UPPS-P Negative Urgency	1.31	0.19	--	--
Barratt Non-planning Impulsivity Subscale	1.23	0.22	--	--
Barratt Total Score	1.59	0.11	1.31	0.19

Note: Covariates included in the models but not shown in this table: sex, reward sensitivity status, baseline mood symptoms (as measured by the BDI or ASRM at Time 1) and number of days between Time 1 and the start of the EMA study

[1]BART = Balloon Analogue Risk Task.

Hypothesis 2

Random intercept (linear) multilevel models were run to test the associations between sleep and circadian rhythm parameters and next-day mood symptoms during the EMA study. All analyses controlled for sex, reward sensitivity status, and baseline mood symptoms (as measured by the BDI or ASRM at Time 1). Skin temperature analyses controlled for ambient (environmental) temperature.

Within-Person Predictions

Actigraphy-measured total sleep time predicted next-day depressive symptoms (B = –.067, $t = -3.22$, $p = .001$), such that fewer minutes of total sleep time were associated with higher levels of depressive symptoms. Actigraphy-measured total sleep time also predicted next-day hypomanic symptoms (B = –.036, $t = -1.99$, $p = .047$), such that fewer minutes of sleep time were associated with higher levels of hypomania.

Between-Person Predictions

Finally, the 20-day average skin temperature acrophase predicted the 20-day average of hypomanic symptoms (B = .621, $t = 2.69$, $p = .007$), such that a later skin temperature acrophase predicted higher levels of hypomania. See Table 4 for detailed results. See the Exploratory Analyses section in Chapter 2 for additional results (e.g., self-reported sleep measurement and affect rating analyses).

Table 4. *Results of multilevel models (sleep and circadian parameters predicting next-day depressive and hypomanic symptoms from Hypothesis 2*

Measure	Depressive symptoms (z)		Hypomanic symptoms (z)	
Within-Person	Coefficient	*p*	Coefficient	*p*
Actigraphy SOL[1]	0.23	0.82	-1.13	0.26
Actigraphy TST[2]	**-3.22±**	**0.001**	**-1.99±**	**0.04**
Skin Temp Acrophase	0.11	0.92	0.47	0.64
DLMO[3]	1.37	0.17	-0.90	0.37
Between-Person				
Actigraphy SOL[1]	0.08	0.94	0.13	0.90
Actigraphy TST[2]	1.15	0.25	-0.18	0.86
Skin Temp Acrophase	-0.09	0.93	**2.69±**	**0.007**
DLMO[3]	0.75	0.45	1.46	0.14

Note: Covariates included in the models but not shown in this table: sex, reward sensitivity status, and baseline mood symptoms (as measured by the BDI or ASRM at Time 1). Skin temperature analyses controlled for ambient (environmental) temperature; SOL[1] = Sleep Onset Latency; TST[2] = Total Sleep Time; DLMO[3] = Dim Light Melatonin Onset; ± = $p < .05$

Hypothesis 3

Random intercept (linear) multilevel models with cross-level interactions were conducted to test the two-way interaction between 1) impulsivity and 2) sleep and circadian rhythm parameters predicting next-day mood symptoms during the EMA study. All analyses controlled for sex, reward sensitivity status, baseline mood symptoms (as measured by the BDI or ASRM at Time 1), and number of days between Time 1 and the start of the EMA study. The results showed a significant cross-level interaction between actigraphy-measured total sleep time and BART score predicting next-day hypomanic symptoms (B = .059, $t = 2.22$, $p = .026$), such that a low BART (–1 SD) score was associated with a negative relationship between total sleep time and hypomanic symptoms ($z = –2.33$, $p = .019$), whereas a high BART (+1 SD) score was associated with a slightly positive relationship between total sleep time and hypomanic symptoms (*z* = .405, *p* = .685, region of significance between –14.76 SD and –.42 SD). See Figure 2 for a plot of the simple slope of this interaction.

One significant interaction was found between Barratt Impulsivity Scale total score and actigraphy-measured sleep onset latency predicting next-day hypomanic symptoms. Barratt Total (B = –.031, *t* = –2.41, *p* = .016) score interacted with actigraphy-measured sleep onset latency to predict hypomanic symptoms, such that shorter sleep onset latency (indicating less time to fall asleep) was associated with more hypomanic symptoms for those who had high Barratt Total scores (–1 SD; *z* = 1.57, *p* = .12), but this relationship was reversed in those who had low Barratt Total scores (+1 SD; *z* = –.46, *p* = .68), region of significance below –1.39 SD and above 4.45 SD). See Figure 3 for a plot of the simple slopes.

Finally, one significant interaction was obtained between impulsivity scores and DLMO time (later DLMO time indicates later circadian phase) predicting to depressive symptoms. UPPS Positive Urgency score interacted with DLMO time to predict next-day depressive symptoms (B = .150, *t* = 1.99, *p* = .047), such that for those with low UPPS Positive Urgency (–1 SD), the relationship between DLMO time and depressive symptoms was weakly negative (*z* = –0.37, *p* = .71, but for those with high UPPS Positive Urgency (+1 SD), the relationship between DLMO time and depressive symptoms was more strongly positive (*z* = 1.85, *p* = .06, region of significance between 1.26 and 51.49). See Table 5 for detailed results and Figure 4 for a plot of the simple slopes.

Table 5. *Results of multilevel models (cross-level interactions between impulsivity measures and sleep and circadian parameters predicting next-day EMA symtpoms) from Hypothesis 3*

Measure	Depressive symptoms (z)		Hypomanic symptoms (z)	
	Coefficient	*p*	Coefficient	*p*
BART				
Actigraphy SOL^{1}	--	--	0.86	0.39
Actigraphy TST^{2}	--	--	**2.22**$^{\pm}$	**0.03**
Skin Temp Acrophase	--	--	--	--
DLMO^{3}	--	--	0.19	0.85
UPPS-P PU				
Actigraphy SOL^{1}	--	--	-0.94	0.35
Actigraphy TST^{2}	--	--	1.08	0.28
Skin Temp Acrophase	--	--	--	--
DLMO^{3}	**0.15**$^{\pm}$	**0.04**	-1.61	0.11
UPPS-P NU				
Actigraphy SOL^{1}	-0.44	0.66	--	--
Actigraphy TST^{2}	-0.82	0.42	--	--
Skin Temp Acrophase	--	--	--	--
DLMO^{3}	0.88	0.38	--	--
Barratt NPI subscale				
Actigraphy SOL^{1}	0.43	0.66	--	--
Actigraphy TST^{2}	-0.44	0.66	--	--
Skin Temp Acrophase	--	--	--	--
DLMO^{3}	1.05	0.30	--	--
Barratt Total score				
Actigraphy SOL^{1}	-0.31	0.76	**-2.41**$^{\pm}$	**0.02**
Actigraphy TST^{2}	-0.48	0.64	1.44	0.15
Skin Temp Acrophase	--	--	--	--
DLMO^{3}	1.02	0.31	0.49	0.62

Note: Covariates included in the models but not shown in this table: sex, reward sensitivity status, and baseline mood symptoms (as measured by the BDI or ASRM at Time 1). Skin temperature analyses controlled for ambient (environmental) temperature; SOL^{1} = Sleep Onset Latency; TST^{2} = Total Sleep Time; DLMO^{3} = Dim Light Melatonin Onset; ± = p < .0

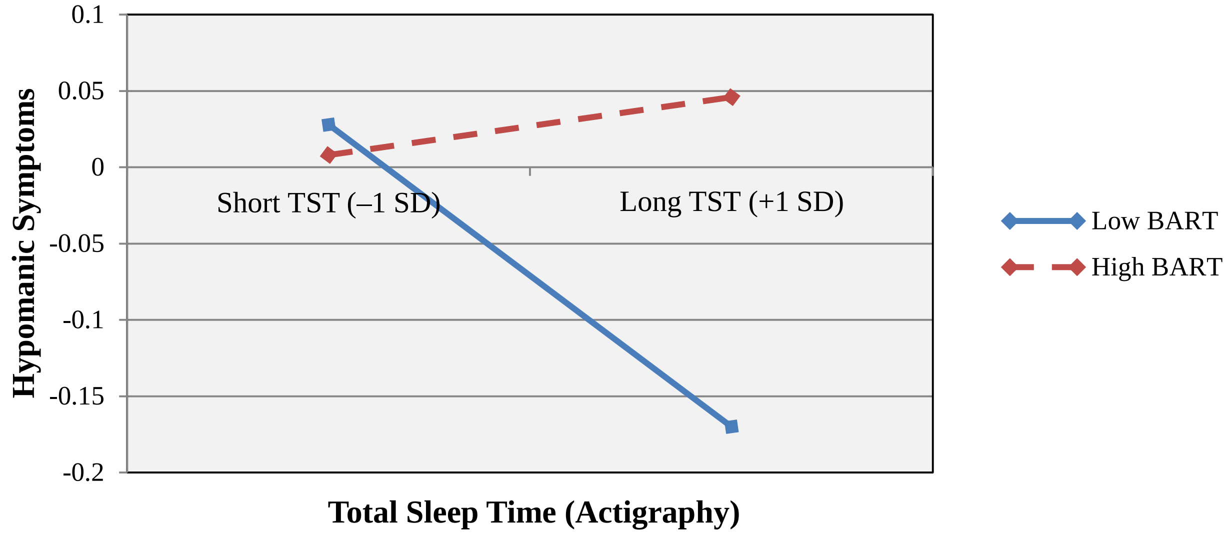


Figure 2. *Plot of simple slopes for BART score and actigraphic total sleep time (TST) interacting to predict next-day hypomanic symptoms and positive affect*

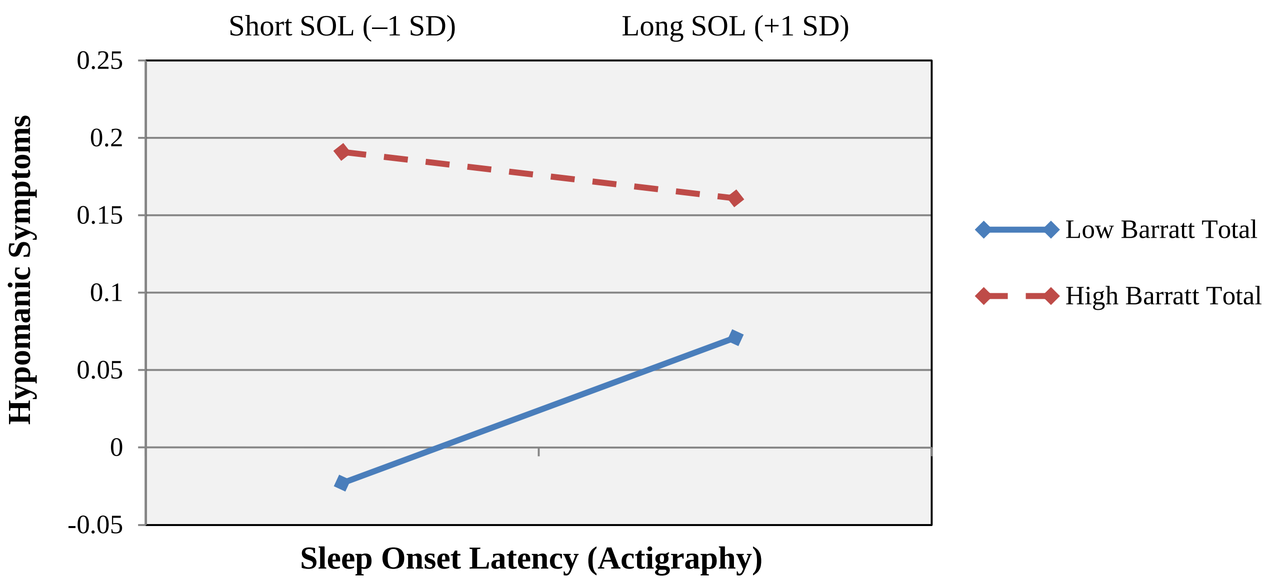


Figure 3. *Plot of simple slopes for Barratt and total score interacting with actigraphy-measured sleep onset latency (SOL) to predict next-day hypomanic symptoms*

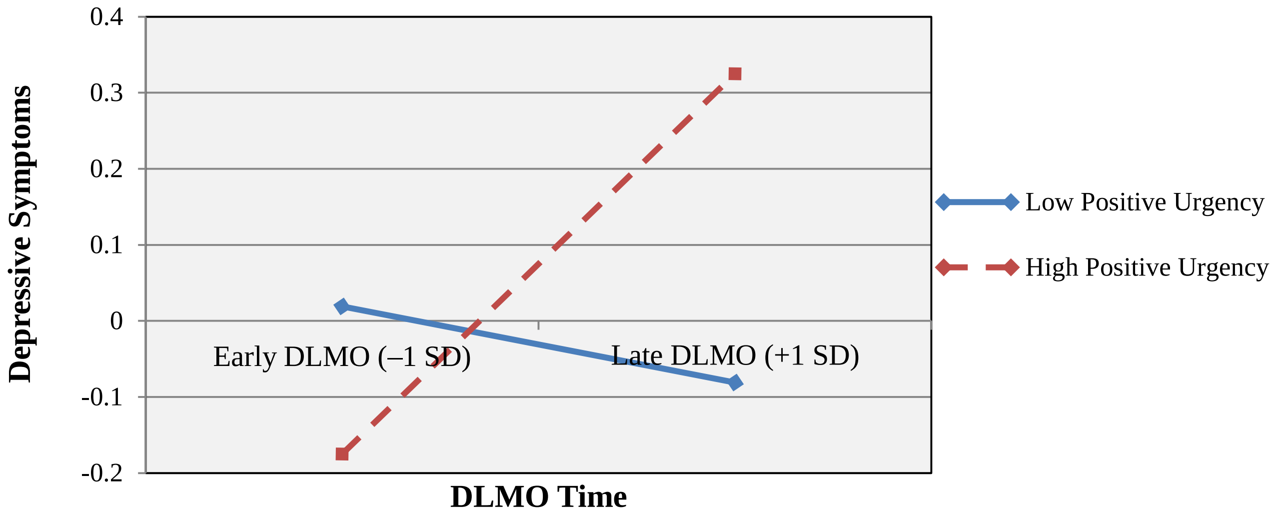


Figure 4. *Plot of simple slopes for total UPPS-P positive urgency interacting with dim light melatonin onset (DLMO) time to predict next-day depressive symptoms*

Hypothesis 4

Logistic regressions examined the two-way interaction between 1) Time 1 impulsivity measures and 2) change scores of sleep and circadian parameters predicting to mood episode diagnoses at the follow-up timepoint after the EMA study. For a summary of average Phase 1 and 2 sleep and circadian parameter values and average change scores, see Table 6. All analyses controlled for sex, reward sensitivity status, baseline mood episode diagnoses, and number of days between the last day of the EMA study and the follow-up timepoint. None of our hypothesized impulsivity or sleep variables significantly ($p < .05$) predicted mood episode diagnoses. Given the low number of depressive and hypomanic episodes at follow-up, it is likely that there was insufficient power to detect any effects.

Linear regressions examined the two-way interaction between 1) Time 1 impulsivity measures and 2) change scores of sleep and circadian parameters predicting to follow-up mood symptoms. All analyses controlled for sex, reward sensitivity status, baseline mood symptoms, and number of days between the last day of the EMA study and the follow-up timepoint. Change scores were calculated by subtracting the average sleep and circadian scores and times of Phase 2 (goal-striving) from the average sleep and circadian scores and times of Phase 1 (baseline).

Two significant interactions predicting to follow-up depressive symptoms were found. Barratt NPI score (B =.414, t = 2.30, p = .021) and Barratt Total score (B = .345, t = 2.97, p = .003) interacted with the DLMO change time to significantly predict first follow-up BDI score. Larger DLMO change times represented later DLMO times during Phase 2 compared to Phase 1 (i.e., later phase during the social rhythm disruption/goal-striving portion of the study). For participants with high Barratt scores (+1 SD), DLMO change time was associated positively with BDI scores (Barratt NPI, $z = 3.99$, $p < .001$; Barratt Total, $z = 2.14$, $p = .032$). For participants with low Barratt scores (–1 SD), DLMO change time was associated negatively with BDI scores (Barratt NPI, $z = -2.32$, $p = .02$; Barratt Total, $z = -1.68$, $p = .09$). See Figure 5 for a plot of the simple slopes.

Two significant interactions predicting to follow-up (hypo)mania symptoms were found. UPPS-P Positive Urgency and Barratt Total scores each interacted with actigraphy-measured sleep onset latency (SOL) change to predict follow-up ASRM score (UPPS-P Positive Urgency, B = –.33, $t = -2.81$, $p = .005$; Barratt Total, B = –.24, $t = -2.09$, $p = .036$). Both interactions showed the same pattern. A large sleep onset latency change indicated that it took participants longer to fall asleep on average during Phase 2 as compared to Phase 1. For participants with a large actigraphy-measured SOL change (+1 SD), there was no relationship between UPPS-P Positive Urgency and ASRM score (UPPS-P, $z = 0.03$, $p = .97$; Barratt Total, $z = -0.03$, $p = .97$). However, for participants with a small SOL change (–1 SD, took participants less time to fall asleep on average during Phase 2 than Phase 1) UPPS-P Positive Urgency was strongly associated with higher ASRM score (UPPS-P, $z = 3.71$, $p < .001$; Barratt Total, $z = 2.84$, $p = .005$). See Figure 6 for a plot of the simple slopes.

In summary, two significant interactions suggested that the combination of being more phase delayed in Phase 2 than Phase 1 and high Barratt impulsivity score predicted higher depression score at follow-up. For (hypo)manic symptoms, two interactions suggested that the combination of falling asleep more quickly in Phase 2 than Phase 1 combined with high UPPS-P positive urgency predicted higher hypomanic symptoms at follow-up. See Table 7 for detailed results.

Table 6. *Summary of sleep and circadian parameter averages from Phase 1 and 2, and change averages*

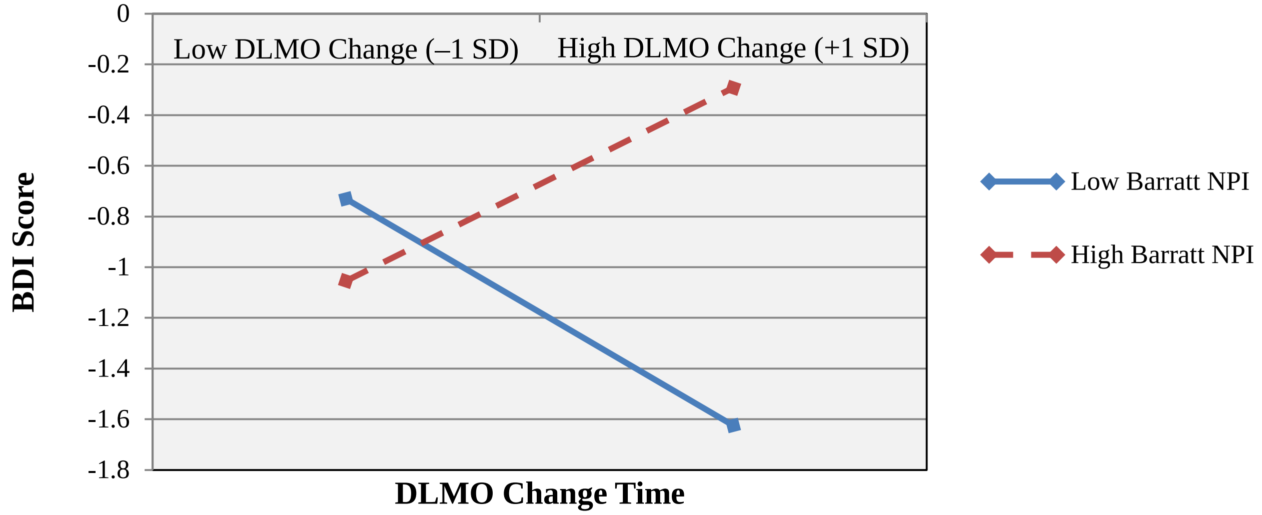
Sleep and Circadian Variables	Phase 1 Means (SD)	Phase 2 Means (SD)	Change Score Means (Phase 2 – Phase1) (SD)
Sleep Onset Latency (SR), mins	38.51 (40.14)	33.40 (33.35)	–5.63 (31.04)
Sleep Onset Latency (Act.), mins	12.21 (9.89)	14.38 (9.39)	2.29 (10.26)
Total Sleep Time (SR), hours	7.36 (1.17)	7.26 (1.16)	– 0.18 (1.13)
Total Sleep Time (Act.), hours	6.95 (1.00)	6.81 (0.94)	–0.14 (0.81)
DLMO Onset Time, hours[1]	21.95 (1.59)	21.99 (1.56)	0.09 (1.03)
Skin Temperature Acrophase[2]	–7.99 (152.71)	1.41 (95.19)	17.46 (178.46)

Note. [1] DLMO = Dim Light Melatonin Onset was measured as melatonin onset time in number of hours and minutes after midnight, [2] Skin Temperature Acrophase, the peak time of skin temperature, was centered around the median value for all participants

Table 7. *Results of linear regressions (interactions between impulsivity measures and sleep/circadian change scores predicting to symptoms at the 3-12 month follow-up timepoint) from Hypothesis 4*

	BDI Score (z)		ASRM Score (z)	
Change Scores	Coefficient	*p*	Coefficient	*p*
BART				
Actigraphy SOL[1]	--	--	0.06	0.95
Actigraphy TST[2]	--	--	0.06	0.96
Skin Temp Acrophase	--	--	1.34	0.18
DLMO[3]	--	--	1.03	0.30
UPPS-P PU				
Actigraphy SOL[1]	--	--	**-2.81**$^{\pm}$	**0.005**
Actigraphy TST[2]	--	--	0.14	0.89
Skin Temp Acrophase	--	--	1.35	0.18
DLMO[3]	--	--	-1.31	0.19
UPPS-P NU				
Actigraphy SOL[1]	0.51	0.61	--	--
Actigraphy TST[2]	1.28	0.20	--	--
Skin Temp Acrophase	1.67	0.10	--	--
DLMO[3]	1.80	0.07	--	--
Barratt NPI				
Actigraphy SOL[1]	0.17	0.87	--	--
Actigraphy TST[2]	0.48	0.63	--	--
Skin Temp Acrophase	0.67	0.50	--	--
DLMO[3]	**2.30**$^{\pm}$	**0.02**	--	--
Barratt Total				
Actigraphy SOL[1]	-0.73	0.46	**-2.10**$^{\pm}$	**0.04**
Actigraphy TST[2]	0.87	0.39	0.98	0.33
Skin Temp Acrophase	1.27	0.20	0.73	0.47
DLMO[3]	**2.97**$^{\pm}$	**0.003**	-0.68	0.49

Note: Covariates included in the models but not shown in this table: sex, reward sensitivity status, and baseline mood symptoms (as measured by the BDI or ASRM at Time 1). Skin temperature analyses controlled for ambient (environmental) temperature; SOL[1] = Sleep Onset Latency; TST[2] = Total Sleep Time; DLMO[3] = Dim Light Melatonin Onset; ± = $p < .05$



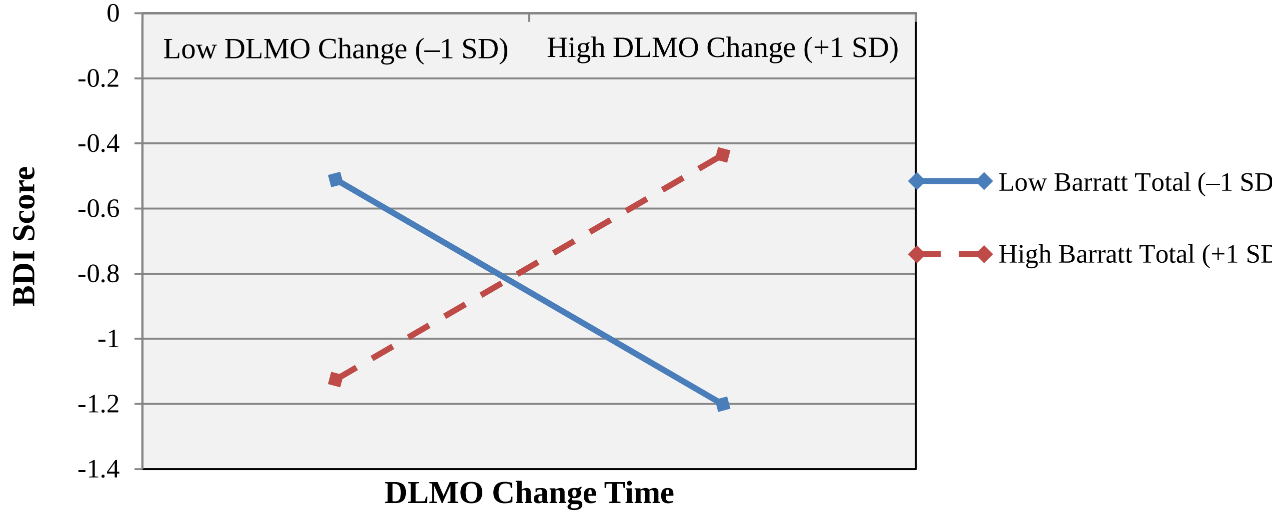
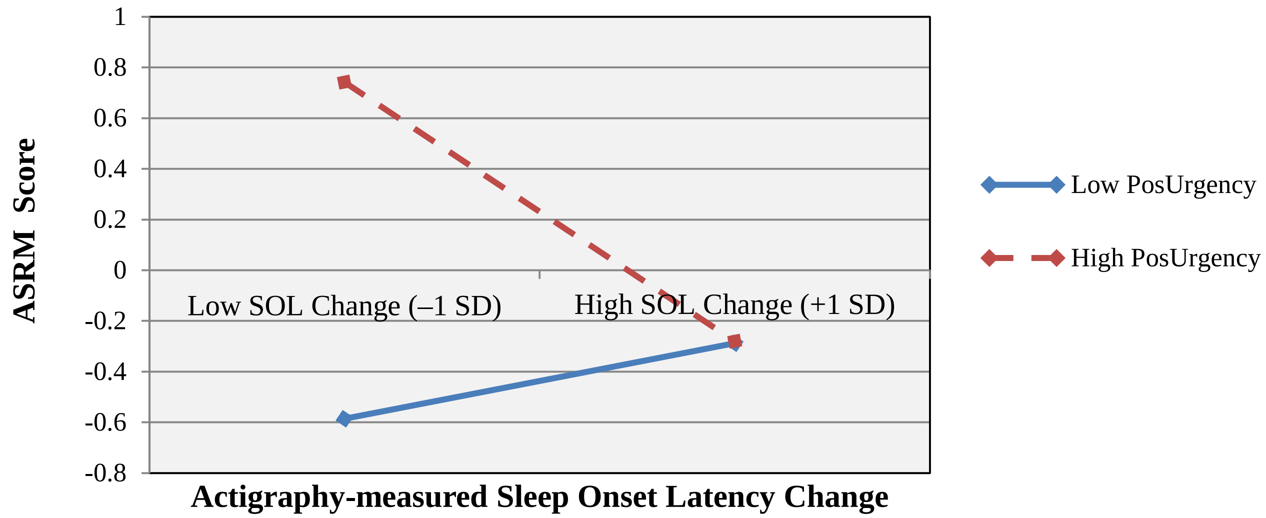


Figure 5. *Plot of simple slopes for Barratt Non-planning Impulsivity (NPI) and total scores interacting with dim light melatonin onset (DLMO) change time to predict Beck Depression Inventory (BDI) score at the follow-up timepoint*



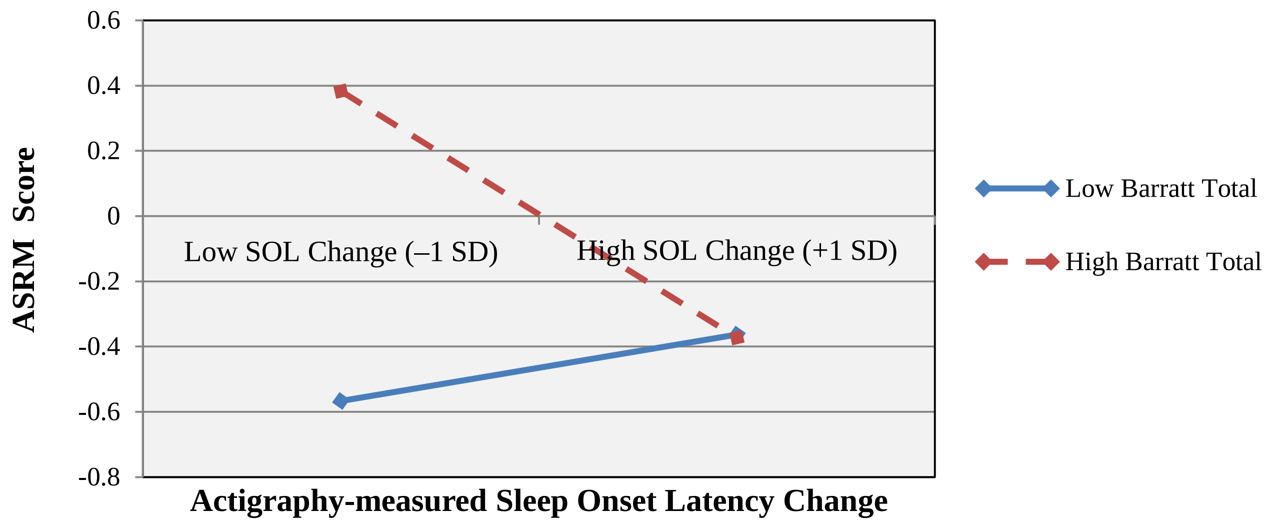


Figure 6. *Plot of simple slopes for UPPS-P Positive Urgency score and Barratt total score interacting with actigraphy-measured Sleep Onset Latency (SOL) change to predict Altman Self-Rating Mania (ASRM) score at the follow-up timepoint*

Discussion

Previous research has indicated that sleep changes, circadian rhythm changes, and impulsivity show interactive effects in healthy individuals (Caci et al., 2005, 2004; Goel et al., 2009; Lowe et al., 2017). Moreover, all three factors have been identified as core features and potential antecedents of bipolar disorder (Alloy et al., 2009; Ng et al., 2015, 2016). However, these dimensions rarely have been examined as interactive risk factors that may contribute to risk for or severity of mood psychopathology. The current study aimed to study the interactive relationships between these features. The results of the present analyses indicate that facets of both impulsivity and sleep and circadian variation are associated (separately and in interaction) with mood symptom severity (both next-day and at 3-12 month longitudinal follow-up). First, none of our hypotheses regarding specific facets of impulsivity predicting mood symptoms were supported. Second, fewer minutes of actigraphic total sleep time predicted more next-day depressive symptoms and hypomanic symptoms. In addition to these main effects, several impulsivity and sleep variables significantly interacted to predict next-day mood symptoms during the EMA study; more minutes of actigraphic total sleep time was generally associated with fewer symptoms, but the presence of high behavioral impulsivity attenuated the relationship between total sleep time and symptoms. Furthermore, shorter actigraphy-measured sleep onset latency interacted with high self-reported impulsivity to predict more severe next-day hypomanic symptoms. Finally, the relationship between later DLMO onset time (later circadian phase) and depressive symptoms was strongly positive in the presence of high impulsivity (UPPS-P Positive Urgency score), as predicted in our hypotheses.

Longitudinal follow-up analyses also revealed several significant interactions. As found during the EMA study, at high levels of impulsivity, larger DLMO change time (later circadian phase in Phase 2) predicted higher depressive (BDI) symptoms at prospective follow-up. Longitudinal analyses with actigraphy-reported sleep onset latency complemented findings for Hypothesis 3; smaller sleep onset latency change combined with high impulsivity scores (UPPS-P Positive Urgency and Barratt scores) predicted higher hypomanic (ASRM) symptoms at follow-up. Finally, exploratory analyses revealed two significant interactions related to self-reported sleep onset latency. These findings contradicted the actigraphy-measured sleep onset latency findings.

We hypothesized that high impulsivity and altered sleep and circadian rhythms would be associated with more mood symptoms and episodes. Moreover, we hypothesized that the combination of altered sleep and circadian rhythms with high impulsivity would interact to predict more depressive and (hypo)manic symptoms. Support for our hypotheses was mixed. Below, we discuss each of the proposed factor's simple associations with mood symptoms/episodes as well as their interactions.

Circadian Rhythm Changes

The findings related to circadian rhythm parameters were generally consistent with one another and with prior literature. Results revealed that the 20-day average of skin temperature acrophase correlated with the 20-day average of hypomanic symptoms and positive affect. Individuals who had later skin temperature peak time also had higher average levels of hypomania and positive affect during the EMA study. This finding is consistent with previous literature demonstrating associations between later circadian phase, eveningness and bipolar disorder (Melo et al., 2017).

Interactions between circadian parameters and impulsivity predicted mood symptoms in both the short-term (next-day) and long-term (3-12 month follow-up) timeframes. Short-term findings indicated that in the presence of high trait impulsivity, later DLMO time was associated strongly with more next-day depressive symptoms. Longitudinal findings were similar. In the presence of high trait impulsivity, participants who experienced a later circadian phase in Phase 2 (social disruption/goal-striving phase) as compared to Phase 1 (baseline) also showed higher depressive symptom scores at follow-up. Given that later DLMO time could represent a more phase-delayed circadian rhythm, and phase delays sometimes have been associated with the depressive pole of bipolar disorder in previous literature (Melo et al., 2017), this result aligns with the findings of prior studies. In our study, the relationship between DLMO time and depressive symptoms only was positive in the presence of high trait impulsivity. Given the well-established link between impulsivity and eveningness or later circadian phase in the literature (Caci et al., 2005, 2004), we can speculate that the combination of the tendency to act impulsively with a later melatonin onset the night before relates to difficulty in next-day mood regulation and stability. Moreover, a larger change in melatonin onset in response to a social rhythm disrupting life event may represent a longer-term risk factor for developing depressive symptoms.

Sleep Alterations

The findings regarding sleep changes and mood are more mixed. One clear main effect of sleep changes on next-day mood emerged. Total sleep time was found to be negatively associated with next-day depressive and hypomanic symptoms. Thus, we could conjecture that sleeping for longer is generally a protective factor against next-day mood symptoms. Of note, this effect is within-person; that is, on nights when a particular individual slept more (compared to his/her own average), he/she had fewer mood symptoms on the following day. Our main effects related to (hypo)mania support the finding that sleep deprivation triggers symptoms of (hypo)mania (Jackson et al., 2003). However, our finding that fewer minutes of sleep also predicts more next-day depressive symptoms has less support in the previous literature.

This main effect must be qualified by a significant interaction between total sleep time and behavioral impulsivity predicting next-day (hypo)mania. High impulsivity attenuated the negative relationship between total sleep time and mood symptoms. This suggests that for those individuals who are high in trait impulsivity, the protective effect of sleep time for (hypo)mania is attenuated or completely mitigated. This finding is deserving of further study, and if replicated, may have clinical implications for the efficacy of regulating sleep time to prevent recurrence of (hypo)mania.

Of note, fewer minutes of sleep and later DLMO time both predicted more next-day mood symptoms for individuals with high trait impulsivity. It is possible that these two findings are related. If melatonin onset time occurs later at night, individuals may have trouble falling asleep until later and trouble obtaining a sufficient amount of sleep. Supporting this theory in our study, fewer minutes of self-reported sleep time was significantly correlated with later DLMO time ($r = –.27$). It is unclear whether one or both of these variables is driving the association with more next-day symptoms.

Several interactions between actigraphy-measured sleep-onset latency and impulsivity predicted short-term and long-term hypomania symptoms. The combination of shorter sleep onset latency (i.e., took a participant less time to fall asleep) and high impulsivity resulted in higher next-day hypomanic symptoms. Similarly, participants who took less time to fall asleep in Phase 2 than Phase 1, combined with high trait impulsivity, showed higher hypomania scores at a longitudinal follow-up. It is not clear why the combination of shorter time to fall asleep and high impulsivity would predict more (hypo)manic symptoms; however, we can conjecture that individuals who fell asleep quickly may have higher sleep debt. Higher sleep debt, in combination with high trait impulsivity, already an established risk factor for developing (hypo)mania (Alloy et al., 2009; Chapman et al., 1984; Johnson, Carver, Mulé, & Joormann, 2013; Kwapil et al., 2000; Lombardo et al., 2012), may combine to result in more mood pathology. Also of note, the findings related to actigraphy-measured total sleep time and actigraphy-measured sleep onset latency were remarkably similar with respect to their interaction with impulsivity and their joint association with mood. Indeed, basic correlational analyses reveal that total sleep time and sleep onset latency are moderately correlated (r = .33). Smaller values on both of these parameters generally suggest that an individual is spending less time in bed. Less time spent in bed combined with high impulsivity seems to predict next-day and long-term positive mood states.

Actigraphy-related sleep onset latency findings (discussed above) contradicted the self-reported sleep onset latency findings that were reported in the Exploratory Analyses section. For those with high impulsivity, self-reported sleep onset latency change was associated positively with (hypo)mania symptoms. Participants who reporting taking longer to fall asleep in Phase 2 than Phase 1 (combined with high impulsivity) reported higher hypomania symptoms. These findings are in the opposite direction of the actigraphy-measured sleep onset latency interaction, and it is unclear why this might be.

However, objective and subjective measures of sleep disturbance rarely correlate well (Ankers & Jones, 2009; Ritter et al., 2012), and that may partially explain the discrepancy in the findings.

Overall, the findings related to sleep alterations were less clear than the findings related to circadian rhythm alterations, and are more complicated to contextualize in the previous literature. We presented some possible interpretations of our findings, but replication and further study will be necessary for better understanding.

Impulsivity

None of our main hypotheses related to impulsivity predicting EMA mood symptoms were supported. However, additional exploratory analyses were run with negative and positive affect outcome variables in place of depressive and hypomanic symptoms. One main effect of impulsivity was found. Negative urgency, or the tendency to act rashly in the presence of negative emotion, predicted negative affect during the EMA study. This may support the hypothesis that the tendency to act rashly may facilitate, worsen, or predispose an individual to negative mood states.

One of our hypotheses, that particular facets of impulsivity (non-planning impulsivity and negative urgency) would be more associated with depression, whereas other facets of impulsivity (risk-taking propensity and positive urgency) would be more associated with (hypo)mania, was largely unsupported. Generally, our findings did provide evidence that elevated impulsivity is related to more mood symptoms (in the context of sleep and or circadian alterations), but many facets of impulsivity appear to be associated with both (hypo)mania and depression.

Strengths and Limitations

Strengths of the current study included the innovative EMA study design, which allowed for naturalistic assessment of the day-to-day relationships between sleep, circadian rhythms, and mood symptoms. One particular strength of collecting multiple observations per individual across days is that this design allows for careful parsing of within-person and between-person variation. We then were able to address two different types of research questions simultaneously: 1) what differences between individuals are associated with risk for mood symptoms?; and 2) for a particular individual, which day-to-day elements are most predictive of mood symptoms?

Additionally, the longitudinal follow-up component of the study design added depth and generalizability to our findings, given that we were able to examine longer-term relationships outside the bounds of the 20-day EMA study. Moreover, both self-reported and objective measures of sleep and circadian rhythm parameters were collected simultaneously, allowing for comparison and cross-validation. Of particular note, our objective and subjective measures of sleep were fairly well-correlated (see Table 1), which is not particularly common in the literature, but allows for more confidence in our sleep measurements. Similarly, both behavioral and self-reported impulsivity measurements were collected, allowing for multiple facets of impulsivity to be separated and analyzed with greater nuance.

Despite these strengths, the study was limited by the small number of mood episodes captured by the longitudinal follow-up. Given the small number of episode occurrences ($n = 6$ for hypomania and $n = 20$ for depression), it is likely that the episode analyses were underpowered. Future studies might endeavor to follow participants over a longer time period in order to gain a higher incidence of mood episode occurrence. Alternatively, future studies should seek to address the same research questions in more severely mood-disordered samples.

Conclusion and Future Directions

Our findings allow for a more nuanced examination of two core features of bipolar disorder and their relationship to mood pathology. With respect to sleep alterations, we chose to examine parameters related to the duration of sleep (total sleep time and sleep onset latency). However, it is equally important to examine the variability of sleep in relationship to mood pathology, as sleep irregularity may be an even more important risk factor for bipolar disorder (Ng et al., 2015). Future studies should strive to examine both duration and variability of sleep and circadian rhythm parameters.

In this study, we chose to examine the relationship of sleep and circadian alterations with next-day mood. However, there also is rationale for examining the relationships of sleep and circadian alterations with mood symptoms that occur two days, three days, or even four days later. It may, for example, take longer than a single day to capture the relationship of reduced sleep or later circadian phase on mood. Future studies should seek to examine these alternative timeframes.

In conclusion, the present study demonstrates preliminary evidence that impulsivity may combine with sleep and circadian rhythm alterations to increase risk for mood symptoms. Our results support the need for more longitudinal research utilizing both subjective and objective measures of sleep and circadian rhythms to examine the dynamic relationship between mood and impulsivity.

CHAPTER 2

ADDITIONAL FINDINGS: EXPLORATORY ANALYSES

Additional Analyses (Related to Main Analyses) Results

Hypothesis 1

Exploratory analyses were conducted using additional impulsivity subscales as predictors and additional positive/negative affect ratings during the EMA study as outcomes. Results indicated that higher UPPS-P Negative Urgency scores significantly predicted greater negative affect during the EMA study (B = .224, t = 2.34, p = .019).

The Barratt Cognitive Instability subscale score positively predicted hypomania (B = .22, t = 2.52, p = .012), as did the Barratt Motor Impulsivity subscale (B = .19, t = 2.09, p = .037). The UPPS-P Positive Urgency Subscale positively predicted negative affect (B = .20, t = 2.04, p = .041). The Barratt Attentional Impulsivity subscale (B = .23, t = 2.50, p = .012) and the Barratt Cognitive Instability subscale (B = .32, t = 3.68, p < .001) positively predicted positive affect. Generally, these additional findings demonstrate that trait impulsivity was positively associated with higher scores at both negative and positive mood poles.

Hypothesis 2

Additional analyses were conducted using self-reported measures of TST and SOL sleep parameters to predict next-day mood symptoms and positive/negative affect during the EMA study. The finding in the main analyses that actigraphy-measured total sleep time predicted next-depressive symptoms was replicated for self-reported total sleep time predicting depressive symptoms (B = –.053, t = –2.06, p = .039). Additionally, the finding in the main analyses that actigraphy-measured total sleep time also predicted next-day hypomanic symptoms was replicated for actigraphy-measured sleep time predicting next-day positive affect (B = –.051, t = –2.89, p = .004), such that fewer minutes of sleep time were associated with higher levels of positive affect. Finally, main results found that the 20-day average skin temperature acrophase predicted the 20-day average of hypomanic symptoms, and exploratory analyses replicated this for positive affect (B = .597, t = 3.53, p < .001), such that a later skin temperature acrophase predicted higher levels of positive affect.

Hypothesis 3

Additional random intercept (linear) multilevel models with cross-level interactions were run to test the interaction between impulsivity and self-reported sleep/circadian rhythm parameters predicting next-day mood symptoms/affect during the EMA study. Exploratory analyses included the addition of self-reported TST and SOL, and included the addition of next-day positive and negative affect ratings. An additional significant cross-level interaction was found between actigraphy-measured total sleep time and BART score predicting next-day positive affect (B = .055, t = 2.37, p = .018), such that total sleep time was negatively associated with positive affect in general, but this negative relationship became stronger for those with low BART scores. This interaction replicates the hypomania interaction in Hypothesis 3 described in the main results section.

Second, an additional significant interaction was obtained between UPPS-P scores and DLMO time (later DLMO time indicates later circadian phase) predicting to positive affect. Barratt NPI score interacted with DLMO time to predict next-day positive affect (B = .123, t = 2.50, p =.013), such that for those with low Barratt NPI score, the relationship between DLMO time and positive affect was weak, but for those with high Barratt NPI score, the relationship between DLMO time and positive affect was strongly positive. This finding is similar to the interaction between UPPS-P score and DLMO time predicting depressive symptoms in the main results section.

Hypothesis 4

Additional linear regressions examined the two-way interaction between 1) Time 1 impulsivity measures and 2) change scores of self-reported sleep and circadian parameters predicting to follow-up mood symptoms (ISS-D [depression] and ISS-A [hypomania] scores).

An additional significant interaction predicting to follow-up depression (ISS-D) score was found. Barratt total score and self-reported total sleep time (TST) change score predicted to ISS-D follow-up score (B = .152, t = 1.96 , p =.049). High TST change score represented participants who slept longer on average during Phase 2 compared to Phase 1. Participants with a high Barratt score showed a positive relationship between TST change score and ISS-D depressive symptoms, whereas participants with a low Barratt score exhibited a negative relationship between TST change score and depression score.

Two additional significant interactions predicting to follow-up (hypo)mania symptoms were found using self-reported (rather than actigraphy-measured) sleep change scores. Self-reported sleep onset latency change showed opposite interaction patterns to the two actigraphy-measured change measures reported above. The interaction between UPPS-P Positive Urgency and self-reported SOL change also significantly predicted first follow-up ASRM score (B= .412, t = 2.68, p = .007), but for participants who reported a large SOL change (e.g., it took longer to fall asleep in Phase 2 than Phase 1), the relationship between UPPS-P Positive Urgency and ASRM score was positive, whereas for participants with a small SOL change (e.g., it took them less time to fall asleep in Phase 2 than Phase 1), the relationship between UPPS-P Positive Urgency and ASRM score was negative. A similar interaction pattern was found for the same predictor variables predicting to ISS-A scores (B = .412, $t = 2.70$, $p = .007$), replicating our finding for predicting to ASRM scores. The interactions containing self-reported sleep onset latency were inconsistent with the actigraphy-measured findings reported in the main results section.

Exploratory Study Hypotheses

Given substantial evidence that chronotype and trait impulsivity are correlated in healthy individuals (Caci et al., 2004, 2005), and that both are associated with risk for bipolar disorder, we explored the relationship between these factors. We explored whether either 1) self-reported trait impulsivity would serve as a partial mediator of the relationship between chronotype (as measured by the Morningness-Eveningness Questionnaire [MEQ]) and mood symptoms in the social rhythm disruption portion of the EMA study, or 2) MEQ score would moderate the association between trait impulsivity and mood symptoms, such that lower scores on the MEQ (indicative of eveningness) would strengthen the association between high trait impulsivity and increased mood symptoms.

Exploratory Analyses Data Analytic Plan

Building on Hypothesis 1, we used static, baseline measures of trait impulsivity and chronotype (Level-2, between-person variables) to predict to averages of (hypo)manic and depressive symptoms during the social disruption phase (Days 6-15) of the EMA study. To test for mediation, we tested both the direct and indirect effect (through trait impulsivity) of chronotype on mood symptoms using the MPlus program (Muthén, Muthén, & Asparouhov, 2016). To test for moderation, we mean-centered chronotype and trait impulsivity to examine their combined associations with depressive and (hypo)manic symptoms during the EMA disruption phase. We controlled for reward sensitivity status and number of days between baseline and start of the EMA study in all analyses for these exploratory questions.

Exploratory Analyses Results

Moderation and mediation models were run to explore the relationship between Time 1 impulsivity, MEQ score, and average daily mood symptoms during Phase 2 (social rhythm disruption portion) of the EMA study. All analyses controlled for sex, reward sensitivity status, baseline mood symptom severity, and number of days between Time 1 and the first day of the EMA study. Planned analyses revealed no significant moderations. Exploratory analyses were conducted using additional impulsivity subscale scores as predictors. A significant interaction was found between the Barratt Cognitive Complexity subscale score and MEQ score predicting depressive symptoms (B = .23, t = 2.15, p = .032), such that for greater eveningness, the relationship between Barratt Cognitive Complexity and depressive symptoms was negative, whereas for greater morningness, the relationship between Barratt Cognitive Complexity and depressive symptoms was positive. The same interaction pattern occurred for the Barratt Cognitive Complexity and MEQ predicting negative affect (B = .24, t = 2.15, p = .032).

Mediation models also were explored. Bootstrapped mediation models were tested to examine both the direct and indirect effect (through impulsivity) of morningness-eveningness on mood symptoms during Phase 2 of the EMA study. Two significant indirect effect models were identified. A significant indirect effect of the relationship between MEQ score and hypomanic symptoms at Phase 2 through Barratt total impulsivity was found (B = -.013, p = .004, CI [-.027, -.015]). However, a significant direct effect in the opposite direction also was present (B = .237, $p < .001$), representing inconsistent mediation. A strong direct relationship between higher MEQ score (morningness) and more severe hypomanic symptoms was found, but the indirect effect (through Barratt impulsivity) suppressed this relationship slightly.

A second significant indirect effect of the relationship between MEQ score and positive affect at Phase 2 through Barratt total impulsivity score was identified (B = -.015, p = .005, CI [-.023, -.009]). Similar to the other significant mediation, a significant direct effect in the opposite direction also was present (B= .300, $p < .001$), representing inconsistent mediation. A strong direct relationship between higher MEQ score (morningness) and more severe hypomanic symptoms was found, but the indirect effect (through Barratt impulsivity) suppressed this relationship slightly. In summary, for both mediation models, a significant indirect effect was identified, but no mediation occurred because the indirect effect was in the opposite direction of the direct effect, acting as a suppressor of the relationship rather than a mediator.

CHAPTER 3

ASSOCIATED LITERATURE REVIEW

Abstract

Two features of bipolar disorder that persist even during episode remission are impulsivity and sleep/circadian rhythm disturbance. These features also are associated with significant morbidity and functional impairment in the disorder. Given that impulsivity and sleep/circadian rhythm disturbance have been shown to have bidirectional influences on one another in healthy samples, it is surprising that few studies explicitly examine their interaction in bipolar disorder. Separate literatures on 1) impulsivity and bipolar disorder and 2) sleep/circadian rhythm disturbance and bipolar disorder are briefly reviewed, followed by 3) a focused review of the large existing literature on the relationship between impulsivity and sleep/circadian rhythm disturbance in healthy individuals. Then, the current article offers a systematic review of seven studies examining the association between impulsivity and sleep/circadian rhythm disturbance in bipolar disorder. Discussion focuses on the substantial limitations present in the existing body of literature and provides methodological and practical suggestions for future research. A concluding section reviews and synthesizes possible mechanisms and theoretical frameworks for understanding the association of these features in bipolar disorder.

Keywords: Impulsivity, sleep disturbance, circadian rhythm disturbance, bipolar disorder, mania, hypomania, depression

Introduction

Bipolar disorder, a serious mental illness consisting of periods of high and low mood, energy, motivation, and behavior, is the sixth leading cause of disability worldwide and afflicts an estimated 60 million people (Murray, Lopez, Harvard School of Public Health, World Health Organization, & World Bank, 1996; World Health Organization, 2006). For many affected, bipolar disorder is a debilitating condition that is associated with significant morbidity, functional impairment, and years of life lost (Merikangas et al., 2007; World Health Organization, 2015). Much impairment occurs during episodes of depression and (hypo)mania, but research also demonstrates that significant deficits and functional impairment remain present even between mood episodes (Robinson et al., 2006b). Individuals continue to show difficulties during interepisode periods in two particular domains: sleep/circadian rhythm disturbance and heightened impulsivity. These deficits contribute significantly to interepisode dysfunction and impairment, and may precipitate risk for episode relapse (Harvey, 2008; Ng et al., 2015; Robinson et al., 2006b; Swann et al., 2001). Patients who are at high behavioral or genetic risk for developing bipolar disorder also exhibit sleep/circadian rhythm abnormalities and heightened impulsivity, suggesting that these domains in particular may be crucial for understanding the mechanisms of bipolar etiology, onset, and course (Alloy et al., 2009; Ng et al., 2015, 2016). Moreover, disturbances in sleep/circadian rhythm systems have been shown to worsen impulsivity (cognitive and behavioral) in healthy individuals (Lim & Dinges, 2010); conversely, heightened impulsivity also has been shown to worsen sleep/circadian rhythm disturbance in healthy samples (Schmidt, Gay, Ghisletta, & Van Der Linden, 2010; Schmidt & Van der Linden, 2009). Given that impulsivity and sleep/circadian rhythm disturbance have 1) been shown to have bidirectional and pernicious interactions in healthy individuals, and 2) are core features of BD, and are often present prior to BD onset and between episodes, it is surprising that few empirical studies to date have examined the interaction between these domains and their effect on BD course, episode onset, and functional impairment.

The current review focuses on the association between sleep/circadian rhythm disturbance and impulsivity in bipolar disorder. We begin by defining terms and briefly reviewing the separate literatures on 1) BD and impulsivity and 2) BD and sleep/circadian rhythm disturbance. Next, following a brief summary and discussion of associations between impulsivity and sleep/circadian rhythm disturbance in healthy individuals, we review studies on the direct association between sleep/circadian rhythm disturbance and impulsivity in BD, highlighting the scarcity of empirical studies published to date. Finally, we suggest possible directions for future research and integration of these features into comprehensive theoretical models of BD.

Bipolar Disorder and Impulsivity

Impulsive behavior is a core symptom of both mania and hypomania in bipolar disorder, characterized in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), as, “Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)” (American Psychiatric Association, 2013). Although this definition of impulsive behavior is explicitly associated with mania, there is a wide range of characterizations associated with the concept of impulsivity; it is a complex and multidimensional construct that has evaded singular definition or classification in the psychopathology literature. We briefly review how impulsivity has been conceptualized and measured by previous researchers, explain how we will define it in this review, and finally provide a short overview of the extant findings on bipolar disorder and impulsivity.

Impulsivity: definition and measurements. The predisposition toward action without thought or reflection is crucial to most definitions of impulsivity. Daruna and Barnes (1993) supplied a formative and influential definition of impulsivity: "impulsivity encompasses a range of actions which are poorly conceived, prematurely expressed, unduly risky or inappropriate to the situation and that often result in undesirable consequences." This definition successfully integrates several important facets of the impulsivity construct; it also demonstrates that any comprehensive definition must be broad and wide-ranging. In recent decades, researchers have attempted to deconstruct impulsivity in order to gain a more specific understanding of its various facets and their relations to psychopathology. Impulsivity has factored into almost every major theoretical model of personality, including Eysenck's Psychoticism-Extraversion-Neuroticism model and the widely used Five Factor Model, although different facets of impulsivity have been given different names (e.g., venturesomeness, sensation seeking, novelty seeking) (Costa & McCrae, 1992; Eysenck & Eysenck, 1987). Barratt and colleagues (Barratt, 1959; Patton et al., 1995) conceptualized impulsivity as a personality dimension and developed the Barratt Impulsiveness Scale (BIS) to measure this trait. They found a three-factor structure for impulsivity that included attentional impulsiveness (the inability to concentrate or focus attention), motor impulsiveness (the tendency to act without thinking), and nonplanning impulsiveness (lack of future planning or foresight) (Bari, Kellermann, & Studer, 2016). Whiteside and Lynam (2001) theorized that there are several separate "pathways" to impulsive behavior, which may be etiologically distinct and related to underlying personality traits. They developed a five-factor model of impulsivity and an accompanying impulsivity scale, the Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale [UPPS-P, (Cyders et al., 2007; Whiteside et al., 2005)], based on dimensions from the Five Factor Model of personality: Positive Urgency and Negative Urgency (related to extraversion and neuroticism, respectively), lack of Perseverance (related to conscientiousness), lack of Premeditation (related to conscientiousness), and Sensation Seeking (related to extraversion). In the UPPS-P model, the two factors related to extraversion (positive urgency and sensation seeking) have significant overlap with the construct of reward sensitivity/behavioral approach system sensitivity. Indeed, some measures of reward sensitivity (e.g., the Behavioral Activation Scale) have been used as measures of trait impulsivity due to their close relation to sensation seeking and disinhibition in positive mood states (Carver & White, 1994). Numerous other attempts to classify and subtype impulsivity have been made, but the field has not reached consensus or narrowed upon a definitive taxonomy of impulsivity.

Another important distinction involves how researchers choose to measure impulsivity: by self-report questionnaire, by laboratory behavioral task, or by directly measuring real-life impulsive behaviors. Customarily, common self-report measures of impulsivity (e.g., BIS, UPPS-P) have focused on capturing a stable, context-independent, characterological form of impulsivity. Conversely, laboratory behavioral measures of impulsivity (e.g., the Go/No-Go paradigm) generally have measured a more motor-based, context-dependent, state-like facet of impulsivity (Fillmore, 2003; Swann, 2010). Common laboratory behavioral tasks of impulsivity broadly can be split into two general categories: 1) measurements of response inhibition, or the suppression of a learned action that is no longer required or context appropriate (as measured by the Go/No-Go paradigm, the Stop-Signal Reaction Time Task, and the Continuous Performance Task, among others); and 2) measurements of delayed gratification, or the ability to resist taking an immediate reward in preference for a later larger reward (as measured by the Delay Discounting Task, among others) (Berg, 1948; Fillmore, 2003; Green, Fry, & Myerson, 1994; Logan, Schachar, & Tannock, 1997; Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956). Sharma and colleagues (2014) conducted a meta-analysis on both self-reported impulsivity questionnaires and laboratory behavioral impulsivity tasks; they found low shared variance between commonly used self-report measures of impulsivity and commonly used behavioral measures of impulsivity, but they found that both types of measurements correlated moderately with the occurrence of real-life impulsive behaviors (e.g., substance use, aggression, gambling). Thus, both methods of impulsivity measurement seem to contribute unique predictive variance to everyday occurrences of impulsive behavior. Given that risky and impulsive real-life behaviors are core symptoms of BD and contribute significant morbidity and impairment, we include several well-known self-report measures and behavioral measures of impulsivity in our inclusion criteria for the purposes of this review.

Impulsivity has been studied extensively in BD using both self-report and behavioral paradigms. Risky and impulsive behaviors also have been measured directly and studied in relation to BD. Although it is outside the scope of this article to provide a comprehensive review of the extensive literature on impulsivity and BD, we provide a focused summary to contextualize our systematic review of impulsivity – sleep/circadian rhythm disturbance associations in BD.

Self-reported impulsivity and BD. Self-reported, context-independent impulsivity has been widely shown to be elevated in mania (Strakowski et al., 2009; Swann, Pazzaglia, Nicholls, Dougherty, & Moeller, 2003), and impulsive behavior is inherent in the diagnostic criteria for mania. Two strong meta-analyses also have found self-reported impulsivity to be elevated during interepisode BD compared to healthy controls (Newman & Meyer, 2014; Saddichha & Schuetz, 2014). There are fewer empirical studies of self-reported impulsivity in the depressed phase of BD, but one study found that a specific subtype of impulsivity, non-planning impulsiveness as measured on the BIS, was elevated in depressed BD compared to euthymic BD, whereas motor impulsivesness was elevated in manic BD (Swann, Steinberg, Lijffijt, & Moeller, 2008).

Self-reported impulsivity in high risk for BD. Less research has been conducted on individuals who are at high genetic or behavioral risk for developing BD, but one study reported that self-reported BIS total score, BIS non-planning impulsiveness, and BIS motor impulsiveness were elevated in unaffected siblings of bipolar I disorder participants compared to healthy controls (Lombardo et al., 2012). Two studies (Alloy et al., 2009; Kwapil et al., 2000) found that participants who were at behavioral high risk for developing BD had elevated scores on a self-report measure of impulsivity, the Impulsive-Nonconformity Scale (Chapman et al., 1984). Johnson and colleagues (2013) found that risk for mania was associated with self-reported impulsivity during positive mood states. Generally, research seems to suggest that trait-like, context-independent impulsivity is elevated across all phases of BD illness, and also may be elevated in individuals at risk for developing BD, suggesting that it not merely a consequence of developing the illness, but also may be a risk factor for BD.

Behavioral impulsivity and BD. The relationship between BD and behaviorally measured, context-dependent impulsivity also has been studied extensively across all mood states. There has been some debate about which behavioral tasks and indices are true measures of impulsivity, but a comprehensive meta factor-analysis by Sharma and colleagues (2014) identified a four-factor structure for behavioral impulsivity: response inhibition (Go/No-Go Task, Matching Familiar Figures Task), impulsive decision making (Delayed Discounting Task), inattention (Stroop Color-Word Test, Continuous Performance Test), and shifting (Wisconsin Card Sorting Test). One meta-analysis found that commission errors on the Go/No-Go Task were elevated in BD compared to healthy controls (Wright, Lipszyc, Dupuis, Thayapararajah, & Schachar, 2014). Several meta-analyses have examined other neurocognitive deficits in euthymic BD compared to healthy controls, and found that behavioral impulsivity (as measured by perseverative errors on the Wisconsin Card Sorting Test) is elevated in euthymic BD (Arts, Jabben, Krabbendam, & van Os, 2008; Kurtz & Gerraty, 2009; Mann-Wrobel, Carreno, & Dickinson, 2011; Robinson et al., 2006a). The meta-analysis by Arts and colleagues (2008) also examined differences between first-degree relatives of BD patients and healthy controls, but found no significant differences in behavioral impulsivity. The Kurtz and Gerraty (2009) meta-analysis examined behavioral impulsivity differentially in mania/mixed states, euthymia, and depressed states, and concluded that impulsivity was increased in manic and euthymic, but not depressed states, compared to healthy controls.

Two other studies examined behavioral impulsivity as it relates to phase of illness in BD. Both studies found that behavioral impulsivity (as measured by commission errors on a variant of the CPT) were elevated in mania but not euthymia or depression relative to healthy controls (Strakowski et al., 2010; Swann et al., 2003). Bora and colleagues (2009), in a another meta-analysis of cognitive deficits in euthymic BD, found that behavioral impulsivity (i.e., response inhibition) deficits were common for both BD patients and their first degree relatives, but their measure of response inhibition was time to completion of the Stroop Color-Word test, which is somewhat nontraditional. On the contrary, a different meta-analysis (Newman & Meyer, 2014) examined effect sizes for behaviorally measured response inhibition (as measured by commission errors on the Go/No-Go task and Continuous Performance Test) in euthymic BD versus healthy controls and found few significant group differences, with the caveat that several of the studies included may have been underpowered. The same meta-analysis also examined behaviorally measured delay of gratification in euthymic BD versus healthy controls and found little evidence for group differences, although only three studies met inclusion criteria for this portion of the meta-analysis.

Overall, the evidence is mixed for elevations of behavioral impulsivity in BD, and results may differ based on the subtype of behavioral impulsivity measured. Some facets of behavioral impulsivity (e.g., deficits in shifting) appear to be consistently elevated across BD states, whereas others (e.g., inattention) only appear to be elevated in mania and/or euthymia. Despite mixed findings, response inhibition deficits appear to be elevated in BD overall, and some researchers have argued that response inhibition deficit may be an endophenotype of BD (Bora et al., 2009). Stronger meta-analyses generally indicate that behavioral impulsivity is elevated in BD, although it may be more beneficial to examine relationships between BD and specific facets of behavioral impulsivity, which appear to be differentially related.

Impulsive, risky, and risk-taking behaviors in BD. Finally, some research has examined the direct link between impulsive/risky behaviors and BD. Hıdıroğlu and colleagues (2013) make an important distinction between risk-taking behaviors and impulsivity; they argue that though risk-taking behavior and impulsivity are closely intertwined, they are not identical constructs. Impulsivity is a predisposition to a pattern of behavior, whereas risky/impulsive behavior is a selected response and is situationally determined (Hıdıroğlu et al., 2013). Using the Balloon Analogue Risk Task, a laboratory task that measures risk-taking behavior, Hıdıroğlu and colleagues (2013) found that risk-taking behavior is elevated in BD and first degree relatives of BD compared to healthy controls. They made the case that risk-taking behavior, rather than impulsivity per se, is a better endophenotype candidate for BD.

One category of risky behavior in BD deserves special consideration: suicidal and self-harming behaviors. Suicide is the leading cause of death in bipolar disorder, and risk for attempting suicide is 20 times higher in BD than in the general population (Tondo, Isacsson, & Baldessarini, 2003). Suicidal or self-harming behaviors can be considered "risky behaviors" because they increase exposure to possible loss or harm (Schonberg, Fox, & Poldrack, 2011). However, suicide and self-harm are not always undertaken impulsively and without prior forethought; unfortunately, some of the most lethal suicide attempts are carefully premeditated. However, one study showed that 24% of suicide attempts were made less than five minutes after individuals made the decision to attempt suicide; generally, findings estimate that one-fourth to four-fifths of total suicide attempts are impulsive (Miller & Hemenway, 2008; Simon et al., 2001). Thus, suicidal and self-harming behaviors will qualify as impulsive behaviors in our systematic review, with the caveat that they are a specific type of impulsive behavior and are almost always undertaken in a negative mood state, thus tightly associated with the negative urgency facet of impulsivity (Anestis & Joiner, 2011).

In summary, a large body of evidence suggests that self-reported (trait) impulsivity is elevated across all phases of BD and also in those at high risk for developing BD. The evidence for elevated behavioral impulsivity in BD is more mixed and mood state-dependent, but findings generally suggest that behavioral impulsivity deficits exist in mania and persist into euthymia, although may not be present in depressive phases of BD. Furthermore, evidence of elevated behavioral impulsivity for individuals at high risk for developing BD is also mixed. Risk-taking behaviors are a built-in symptom of mania, but one study showed that risk-taking behavior also is elevated in euthymia and individuals at high genetic risk. Suicide, a specific type of risky behavior, also is highly prevalent in BD.

Having reviewed the association between impulsivity and BD, we next briefly review a separate literature on sleep and circadian rhythm disruption in BD, with the aim of integrating these literatures in the subsequent systematic literature review and discussion.

Sleep and Circadian Rhythm Disturbance in Bipolar Disorder: Overview

Disturbance in the sleep-wake cycle is a prominent characteristic of BD and is thought to play a crucial role in the pathogenesis of the disorder (Alloy, Nusslock, &

Boland, 2015; Harvey et al., 2009). Sleep disturbance in the form of insomnia, hypersomnia, and reduced need for sleep are core symptoms of BD, and are reported in 15-100% of BD patients even during remission of acute depression or (hypo)mania (American Psychiatric Association, 2013; Boland & Alloy, 2013). Genetic, self-report, and physiological evidence suggests that circadian rhythm dysregulation more generally is associated with BD in numerous ways; indeed, abnormality in circadian rhythms has been proposed as an endophenotype of BD (Lenox et al., 2002). Below, we present a brief definition of sleep and circadian rhythm disturbance, discuss measurement of these constructs, and provide an overview of the literature on both circadian rhythm and sleep disturbance in BD.

Process S and Process C in BD. Human sleep-wake regulation is thought to be influenced by two separate biological processes, a sleep homeostatic process (Process S) and a circadian process (Process C) (Colten, Altevogt, & Institute of Medicine (U.S.), 2006; Harvey, 2008). Process S is a homeostatic process that functions similarly to hunger, inasmuch as the drive to sleep (i.e., "sleep debt") increases as time spent awake grows longer, and is relieved only by a consolidated period of sleep (including some combination of light sleep, deep sleep, and rapid eye movement (REM) sleep) (Colten et al., 2006). Process C is the process by which circadian rhythms are regulated and entrained, and it has separate neurobiological underpinnings from Process S. In humans, the circadian pacemaker is responsible for regulating endogenous biological rhythms of approximately 24 hours. Many human biological functions fluctuate in a 24-hour cycle (e.g., temperature, blood pressure, hormone levels), and these fluctuations are largely controlled by the circadian clock in the suprachiasmatic nucleus [SCN; (Roenneberg et al., 2007)], although there are peripheral clocks in other brain areas and tissues that can be synchronized or desynchronized with the main clock in the SCN (Cermakian & Boivin, 2009). The circadian clock is capable of operating without input from external sources, but also is entrained by external photic and non-photic cues, such as light input to the eyes, auditory input, and social rhythms (Jeanne F. Duffy & Wright, 2005; Mistlberger & Skene, 2004; Mrosovsky, 1996). However, light is the strongest element of human circadian rhythm entrainment (Jeanne F. Duffy & Wright, 2005).

Process S and Process C – measurement and methodological issues in BD. Process S and Process C both operate simultaneously to regulate arousal and sleep/wake patterns. Although these processes have separate neurobiological underpinnings, it is difficult to parse apart their unique effects in humans because they are highly intertwined and both influence sleep-wake regulation, which has led to a muddled picture of their separate roles in BD. Researchers should strive as much as possible to differentiate between measurement of circadian rhythm disturbance and sleep disturbance, given that their associations with BD may be distinct and unique. Circadian rhythms are best measured directly by capturing melatonin onset time and by continuously measuring temperature to examine peaks, troughs, and amplitude (Buhr, Yoo, & Takahashi, 2010; Pandi-Perumal et al., 2007). Sleep parameters are best measured by a combination of objective (e.g., polysomnography, actigraphy) and subjective (e.g., sleep diary) indices of sleep (Harvey et al., 2009). Sleep disturbance, a chronic feature of BD, can be caused by an intrinsically or externally driven circadian rhythm disruption, a disruption in Process S, or a mismatch between timing or amplitude of Process C and Process S. It is also important to note that sleep disturbance encompasses insomnia, hypersomnia, and sleep deprivation. Insomnia is the subjective experience of deficient sleep, whereas sleep deprivation is an objective measure of sleep decrement (Harvey et al., 2009).

Definitions. Our review uses ‘sleep disturbance’ as a term that encompasses all three aforementioned constructs: insomnia, hypersomnia, and sleep deprivation. We also utilize a broad definition of ‘circadian rhythm disturbance’, which can encompass a deviation from one’s own circadian rhythm or a large deviation from the population norm (e.g., advanced or delayed circadian phase); moreover, the disturbance can be caused by an external perturbation or by an intrinsic abnormality in the timing functions of the individual’s circadian pacemaker.

Sleep Disturbance and Bipolar Disorder

Insomnia and BD. Ng and colleagues (2015) conducted a meta-analysis on sleep-wake disturbance in euthymic BD, comparing patients with euthymic BD to patients with primary insomnia and healthy controls. They found that euthymic BD appeared worse than healthy controls on many subjective and objective sleep-wake variables, and similar to adults with primary insomnia, including similar sleep onset latency, daytime sleepiness, and time spent in bed. A study comparing adults with euthymic BD and patients with insomnia found that the two groups had comparably higher levels of dysfunctional beliefs about sleep than a healthy sleep group (Harvey, Schmidt, Scarnà, Semler, & Goodwin, 2005).

Hypersomnia and BD. Hypersomnia is a symptom of atypical depression, and it is a more prevalent symptom in BD than in major depressive disorder (MDD); indeed, a review found that prevalence rates of hypersomnia in BD-I and BD-II ranged between 17-78% (Kaplan & Harvey, 2009). The same review summarized evidence that hypersomnia was an independent predictor of BD-II, suggesting that it might reliably differentiate MDD and BD-II. Regarding its relation to BD course, hypersomnia is more often present during depressed phases of BD than euthymic or manic phases (Kaplan & Harvey, 2009). However, one actigraphy meta-analysis found that BD patients had a longer sleep duration regardless of mood state than healthy controls (De Crescenzo, Economou, Sharpley, Gormez, & Quested, 2017). During euthymia, BD participants also show significantly longer total sleep time (TST) and spend more time in bed (TIB) than healthy sleepers or patients with primary insomnia. Additionally, their TST is more variable (Ng et al., 2015; Ritter et al., 2012).

Sleep deprivation and BD. A large body of experimental evidence demonstrates that one night of laboratory sleep deprivation rapidly reduces depressive symptoms and suicidality in depressed BD, although this effect usually remits after one night of recovery sleep (Barbini et al., 1998; Benedetti et al., 2014; Wu & Bunney, 1990). Conversely, sleep deprivation serves as a possible pathway and reliable prodrome to the onset of (hypo)mania in BD (Plante & Winkelman, 2008; Wehr, Sack, & Rosenthal, 1987).

Other sleep disturbance in BD. Two meta-analyses (De Crescenzo et al., 2017; Ng et al., 2015) found that sleep in BD was more variable and had a "more disturbed pattern" than in healthy controls, based on a combination of subjective and objective measures.

Sleep disturbance and mood state or BD prodromes. There is some evidence that certain types of sleep disturbance may precede (hypo)mania episodes in BD. A review of depression and mania prodromes found that sleep disturbance was the most common prodrome of mania, occurring in 80% of participants (Jackson et al., 2003). The Ng and colleagues (2015) meta-analysis also examined sleep disturbance in participants at high risk for developing BD, and they concluded that there is not currently enough cumulative evidence to draw strong conclusions about sleep disturbance in participants at high risk for developing BD. However, several individual studies have compared individuals at high risk for BD to healthy controls, and have found more self-reported (Ritter et al., 2012) and objectively measured (Ankers & Jones, 2009) sleep disturbance, although these findings are preliminary.

Overall, it appears that sleep disturbance is related to bipolar disorder course and episode onset. Hypersomnia appears to be more prevalent in depressive phases of BD, whereas insomnia is present in euthymic BD and depressive phases. Sleep deprivation has been associated with rapid remission of depressive and suicidal symptoms, and has been shown to trigger onset of (hypo)mania episodes. Although it is possible that sleep disturbance also is present in participants at high risk for BD, currently, there is insufficient evidence to draw clear conclusions and the few existing studies are mixed, with some showing that high-risk resembles a healthy control group, whereas others show that it is more similar to BD.

Circadian Rhythm Disturbance and Bipolar Disorder

Chronotype and BD. Chronotype, also known as circadian preference, is a self-reported characteristic of between-person variation in circadian rhythmicity. Individuals vary on a spectrum ranging from ‘morning chronotype’ to ‘evening choronotype’ on this dimension; those who are classified as ‘evening chronotypes’ report preference for later bedtimes, waketimes, and completion of demanding activities during the afternoon/evening hours (Adan et al., 2012). Conversely, those categorized as 'morning chronotypes' endorse preference for earlier bedtimes, earlier waketimes, and earlier completion of demanding activities (e.g., exercising, working, or studying) (Adan et al., 2012). Self-reported eveningness also has been linked to circadian phase delay, a physiological measure of later clock-time circadian rhythm peaks (e.g., melatonin onset and cortisol rhythm) (Adan et al., 2012). Recently, Melo and colleagues (2017) conducted a meta-analysis on the role of chronotype in BD, and found that BD participants generally tended to report higher levels of eveningness in both depressive and euthymic mood states, although this relationship was more pronounced in depressive states, and there were too few studies on mania to draw conclusions. Another meta-analysis was conducted on chronotype and circadian phase in individuals at high risk for BD, and no differences were found for chronotype in BD risk compared to healthy participants (Matias Carvalho Aguiar Melo et al., 2016). A recent study (Kanagarajan et al., 2018) found higher prevalence of evening chronotype in patients with BD than the population norm, and also found that eveningness was associated with insomnia in BD.

Melatonin and BD. The physiological correlate of self-reported eveningness is delayed circadian phase, which is partially controlled by melatonin release. Abnormalities in the release and timing of the hormone melatonin also have been observed in BD. Melatonin, a hormone secreted by the pineal gland, is released in response to darkness, aids with sleep onset and external circadian rhythm entrainment, and follows a roughly 24-hour cycle; peak onset typically occurs between 0:00 and 06:00, during the darkest hours of the early morning (Brzezinski, 1997). In a review of circadian rhythm disturbance in BD, Alloy, Ng, Titone, and Boland (2017) noted that certain aspects of melatonin secretion, such as time of release, may be state-related; for instance, advanced or earlier release of melatonin may be associated with manic states, whereas delayed melatonin onset has been associated with depressed and euthymic states. They also noted evidence that amount of melatonin secreted may be low across mood states in BD compared to healthy controls, although evidence remains mixed (Alloy et al., 2017).

Lithium and circadian period in BD. Administration of the mood stabilizing drug lithium shows efficacy in treating mood symptoms in a portion of patients with BD; there is limited evidence that one mechanism of lithium action may be slowing of the circadian period (i.e., circadian cycle length) (Abe, Herzog, & Block, 2000). In one case series study of seven BD patients, five evinced a fast-running circadian cycle, and the administration of lithium slowed their circadian periods (D. F. Kripke, Mullaney, Atkinson, & Wolf, 1978).

Circadian genes and BD. Researchers have located numerous genes that control circadian rhythm expression and also are modestly associated with BD; in their review, Alloy and colleagues (2017) identified the circadian locomotor output cycles kaput (CLOCK) gene (Daniel F Kripke et al., 2009; Shi et al., 2008), GSK3-β gene (Benedetti et al., 2003), PER3 gene (Nievergelt et al., 2006), ARNTL gene (Nievergelt et al., 2006), TIMELESS gene (Mansour, Monk, & Nimgaonkar, 2005), and NR1D1 ROR gene (Lai et al., 2015) as having associations with bipolar spectrum disorders. Given that gene expression is moderated by environmental input, it is important to note that some circadian-regulating genes only may confer risk for BD when coupled with environmental stressors, as shown by Benedetti and colleagues (2015); in depressed patients with BD, they discovered an interaction between the *C carriers of the CLOCK rs1801260 gene polymorphism and exposure to stressful life events, such that patients who were *C carriers and were exposed to high levels of stressful life events had greater history of suicide attempts.

Social rhythm disturbance and BD. As stated above, circadian rhythms are partially entrained by external social cues, such as mealtimes, routines, and social contact (Mistlberger & Skene, 2004). Thus, it follows that social rhythm disruption may disrupt external entrainment of circadian rhythms. The social zeitgeber theory (Ehlers, Frank, & Kupfer, 1988; Grandin, Alloy, & Abramson, 2006) of mood disorders proposes that a disruption of daily social rhythms can trigger disruptions to the circadian system, producing mood symptoms, episodes, and other changes in neurotransmitters. As of yet, no direct empirical test of the causal link between social rhythm disruption and circadian rhythm disruption exists, although a growing body of literature suggests that self-reported and interviewer-rated social rhythm disturbance is associated with (Jones, Hare, & Evershed, 2005; Pinho et al., 2016) and, in some cases, prospectively predicts recurrence of depressive and (hypo)manic symptoms and episodes in BD (Malkoff-Schwartz et al., 2000, 1998; G. H. Shen, Alloy, Abramson, & Sylvia, 2008; Sylvia et al., 2009). Finally, the large body of empirical support that has accrued for the efficacy of Interpersonal and Social Rhythm Therapy for BD (Crowe, Beaglehole, & Inder, 2016; Frank, Swartz, & Boland, 2007), a therapy that combines aspects of interpersonal therapy with social rhythm regulation and stabilization, demonstrates that the severity of BD mood episodes and symptoms can be improved by stabilization of social routines and rhythms (Frank et al., 2005; Swartz, Frank, & Cheng, 2012).

In summary, circadian rhythm abnormalities and disturbances in external entrainment appear pervasive in BD. Several genes related to circadian rhythm regulation have shown modest associations with BD, and the trait-like preference for eveningness, suggesting circadian phase delay, also is linked to BD. Melatonin release also appears to be delayed in depressive and euthymic phases of BD and advanced in manic phases of BD, while several efficacious treatments for BD (e.g. lithium, IPSRT) may have their action through circadian-related pathways.

Sleep/Circadian Disturbance and Impulsivity in Healthy Individuals

Thus far, we have separately reviewed the literatures on impulsivity and sleep/circadian rhythm disruption in BD. Unfortunately, the literature examining both of these constructs and their relation to BD is very limited. However, a large body of research in healthy individuals exists demonstrating that sleep disturbance and impulsivity have bidirectional effects on one another – ostensibly, critical review of this literature may provide a framework for how these important features might interact in BD. The literature in healthy individuals is vast and wide-ranging, so we do not attempt to provide a comprehensive review here, but instead highlight a few key aspects of how these two variables affect one another in healthy people.

` One line of research concerns the effect of acute and long-term sleep restriction or deprivation on impulsivity. A recent meta-analysis of the neurocognitive effects of sleep restriction (Lowe et al., 2017) examined performance on inhibitory control and impulsive decision-making tasks following experimentally induced sleep deprivation. Results found a significant negative effect of sleep deprivation on performance on inhibitory control tasks (e.g., Stroop, CPT), but no significant effect of sleep deprivation on performance on impulsive decision-making tasks (e.g., BART, Delay Discounting). In an earlier comprehensive review of the neurocognitive effects of sleep deprivation, Goel and colleagues (2009) also noted a decrement in inhibitory control following sleep deprivation; however, they noted high interindividual variability in the effect of sleep deprivation on inhibition. In a meta-analysis of the effects of short-term sleep deprivation on cognition, Lim and Dinges (2010) found that inhibitory control suffered a decrement after just one night of full sleep deprivation. Sleep deprivation clearly affects inhibitory control, but one study (Mckenna, Dickinson, Orff, & Drummond, 2007) examined the effect of sleep deprivation on a different facet of impulsivity – risk-taking decisions. Results indicated that 24 hours of sleep deprivation led participants to be more willing to take a risk than they ordinarily would on a behavioral risk-taking task when considering a gain. Although sleep deprivation is not an explicit criterion of BD, it becomes highly relevant when considering that a common symptom of (hypo)mania is “reduced need for sleep;” however, an individual’s perception of reduced need for sleep to feel well-rested does not necessarily indicate that they need less sleep to maintain good cognitive functioning (American Psychiatric Association, 2013). Given the evidence in healthy controls that reduced sleep worsens impulsivity, it is reasonable to speculate that reduced sleep and impulsivity could have pernicious bidirectional effects on the onset, clinical course, and level of impairment in BD.

Notably, several studies have begun to parse the neural correlates of the relationship between sleep deprivation and impulsivity. One neuroimaging study (Chuah, Venkatraman, Dinges, & Chee, 2006) examined the neural basis of decrements in performance on the Go/No-Go task following 24h of sleep deprivation as compared to a within-subjects rested baseline; results indicated that regardless of decrement in behavioral performance on the Go/No-Go task, bilateral ventral and anterior PFC activation was decreased during the task as compared to rested wakefulness. However, neural activity in right ventral PFC during rested wakefulness could distinguish individuals able to maintain inhibitory efficiency following sleep deprivation from those who performed poorly following sleep deprivation. Another neuroimaging study (Venkatraman, Chuah, Huettel, & Chee, 2007) utilized a gambling task to study the neural basis of risky decisions following sleep deprivation. Results indicated that 24 hours of sleep deprivation resulted in greater activation in the right nucleus accumbens following high risk choices, and also resulted in reduced activation for losses in the insular and orbitofrontal cortices. These results suggest that sleep deprivation may increase risky decision making by attenuating neural sensitivity to loss and elevating expectation of reward following high risk choices. It is exciting that researchers have begun to parse the neural basis of the relationship between impulsivity and sleep deprivation; preliminary findings highlight decrements in the prefrontal cortex following sleep deprivation and increased activation in limbic/reward-related areas of the brain.

Another salient line of research in healthy controls concerns the well-established association between evening chronotype and self-reported trait impulsivity. A comprehensive review by Adan and colleagues (2012) concluded that multiple facets of trait impulsivity were associated with higher levels of eveningness. Several studies have explored which facets of impulsivity are most associated with eveningness; one such study (Adan, Natale, Caci, & Prat, 2010) used a self-report measure of functional and dysfunctional impulsivity to examine their differential relationship to eveningness. They found that morning-type participants demonstrated lower dysfunctional impulsivity scores, and that higher dysfunctional impulsivity scores were found for men who had neutral or evening chronotypes. However, no differences between men and women were found in the morning chronotype group. They concluded that morning chronotype may be viewed as a protective factor against dysfunctional impulsivity, especially for men. Another study explored impulsiveness as a facet of novelty seeking, and found a significant relationship with the tendency to plan activities in the evening (Caci et al., 2004). A second study by the same research group (Caci et al., 2005) used the Impulsiveness-Venturesomeness-Empathy questionnaire (Caci, Nadalet, Baylé, Robert, & Boyer, 2003) to examine differential relationships between impulsivity and venturesomeness (a facet of sensation seeking). Their findings suggested that impulsivity, but not venturesomeness, was related to low morningness in healthy participants. More recently, one study used structural equation modeling to examine personality traits in relation to circadian preference, and found that all associations between eveningness and the Big Five personality traits was explained through impulsivity/sensation seeking pathways (P. M. Russo, Leone, Penolazzi, & Natale, 2012). Finally, a recent study by Kang and colleagues (2015) examined the relationship between multiple facets of impulsivity and eveningness; they examined self-reported impulsivity as measured on the Barratt Impulsiveness Scale, self-reported disinhibition as measured on the Sensation Seeking Scale, and behavioral impulsivity as measured by Go/No-Go task performance, and found that eveningness was associated with all three measures of impulsivity, although only at the trend level for behavioral impulsivity. Considered together, these studies provide strong evidence for an association between impulsivity and evening circadian preference. As noted above, evening circadian preference has been linked to a circadian phase delay. Given the separate, but compelling, associations between circadian rhythm abnormalities, impulsivity, and BD, it is possible that this association affects the course, severity, or onset of BD.

In summary, in healthy individuals, evidence supports that both sleep disturbance and circadian rhythm abnormalities are directly linked to impulsivity and disinhibition, although causal relations remain unclear. However, the sleep restriction/deprivation studies, which directly manipulate sleep, provide stronger evidence for potential causal effects of sleep disturbance on promoting impulsivity. Next, we review the small body of literature that directly examines the associations between impulsivity and sleep/circadian rhythm disturbance in BD.

Method

For the purposes of this systematic review, impulsivity encompassed traditional measures of self-reported impulsivity (Behavioral Activation System Scale, Barratt Impulsiveness Scale, Dickman Impulsivity, Eysenck Personality Questionnaire, Eysenck Impulsivity Inventory, Multidimensional Personality Questionnaire, UPPS-P Impulsive Behavior Scale, and Impulsive Nonconformity Scale), behavioral impulsivity (as measured by the Go/No-Go task, Matching Familiar Figures Task, Circle Tracing Task, Stop Signal Reaction Time Task, Wisconsin Card Sorting Task, Delayed Discounting tasks, Balloon Analogue Risk Task, Stroop Color-Word Test, and Iowa Gambling Task), and risky behaviors (aggression, alcohol use, drug use, gambling, risky sexual behavior, and suicidal behavior). Sleep and circadian rhythm disturbance were defined as objectively measured (polysomnography, actigraphy, melatonin, skin temperature) or subjectively measured (sleep diary, self-report, or clinician-administered interview) intraindividual deviation or interindividual deviation from normal (individual baseline or deviation from a healthy control group). To be included in the review, articles had to report on any cross-sectional or prospective association between impulsivity and any sleep or circadian-rhythm related variable in a sample of participants diagnosed with bipolar disorder. Studies were identified by systematic searches in PyscInfo and PubMed using a wide range of terms in order to be as comprehensive as possible. This was necessary given that impulsivity is a heterogeneous construct that has been defined and measured in many different ways. Search terms included combinations of the following sleep and circadian rhythm terms: sleep, sleep disturbance, rhythm, circadian, circadian rhythm, biological rhythm, chronotype, and eveningness with the following impulsivity terms: impuls, sensation seeking, novelty seeking, planning, disinhibition, constraint, inhibition, inattention, behavioral inhibition system, behavioral activation system, barratt impulsiveness, dickman impulsiveness, emotionality, activity level, and sociability, eysenck personality, eysenck impulsiveness, multidimensional personality, upps impulsive behavior, impulsive nonconformity, go no-go, matching familiar figures, circle tracing, stop signal reaction time, wisconsin card sorting, delay of gratification, balloon analogue risk, stroop, iowa gambling, risky behavior, risk-taking behavior, gambling, risky sexual behavior, substance use, suicidal behavior with the following bipolar disorder terms: bipolar, mania, hypomania, manic, hypomania, hypomanic.

Results

The searches in PubMed and PsycINFO identified 274 unique articles. The first author reviewed all abstracts and identified 244 that clearly did not meet the inclusion criteria for examining the relationship between sleep/circadian rhythm disruption and impulsivity in bipolar disorder. The first author read the 30 remaining articles in full to determine their eligibility for the systematic review. Articles were excluded if 1) the impulsivity measure or sleep/circadian rhythm measure was not explicitly defined, thus preventing the author from making a judgment about its validity, or 2) the methods and diagnostic criteria for making the bipolar disorder diagnosis were not clearly defined. The author identified one additional article outside of the PsychInfo and PubMed search that met inclusion criteria. Seven unique articles were identified as meeting criteria for inclusion in our systematic review (see Table 1).

Discussion

Systematic review of the literature revealed that a limited number of studies, all published within the past eight years, have examined the association between impulsivity and sleep/circadian rhythm disturbances in bipolar disorder. In this section, we provide a detailed summary of the seven selected articles, recommend directions for future research, and discuss the theoretical models that may explain the association.

Of the seven studies included in our review, two examined self-reported impulsivity, two examined behavioral impulsivity, and three examined risky behaviors directly. In addition, two studies examined biological rhythm disturbance and five studies assessed sleep disturbance.

One methodologically strong study (M. Russo et al., 2015) examined the role of sleep disturbance, overall sleep quality, and a self-report measure of trait impulsivity in a bipolar spectrum disorder sample (N = 117). Participants were recruited from two outpatient psychiatry sites and were diagnosed with bipolar I disorder, bipolar II disorder, or bipolar disorder not otherwise specified using the Structured Clinical Interview for the *DSM-IV* (SCID) (M. B. Spitzer, Gibbon Miriam, & Williams, 2002). Participants were euthymic at the time of study, as measured by a score of less than 15 on the Hamilton Depression Rating Scale (Hamilton, 1967) and a score of less than 8 on the Clinician Administered Rating Scale for Mania (Altman, Hedeker, Janicak, Peterson, & Davis, 1994). For measures of sleep disturbance, participants completed two self-report questionnaires: 1) the Epworth Sleepiness Scale [ESS; (Johns, 1991)], an 8-item questionnaire that is a measure of daytime sleepiness, and 2) the Pittsburgh Sleep Quality Index [PSQI; (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989)], a self-report instrument measuring the quality and pattern of adult sleep, generating seven subscales. Impulsivity was measured with the Barratt Impulsiveness Scale (BIS; Barratt, 1959; Patton et al., 1995). Russo and colleagues examined bivariate correlations of the BIS score with PSQI and EPP scores. Higher impulsivity score was positively correlated with the sleep disturbance subscale of the PSQI (r = .31, medium effect size) and the PSQI total score (r = .33, medium effect size). Then, they used a path analysis technique to examine hypotheses about the causal relationship between impulsivity, sleep disturbance, and cognitive deficits as measured by the MATRICS neuropsychological test battery (Nuechterlein et al., 2008). The best fitting model for working memory deficits showed that heightened trait impulsivity had a positive effect (r =.24) on PSQI total sleep quality; worsened sleep quality, in turn, had a negative effect on working memory (r = -.27), creating an indirect pathway for trait impulsivity on working memory through sleep quality. Notably, trait impulsivity also had a direct effect on working memory, but was associated with higher working memory scores (r = .26). Thus, the direct and indirect effects of impulsivity were in opposite directions. For the social cognition model, heightened impulsivity predicted higher levels of sleep disturbance (*r* = .22), which, in turn, predicted poor social cognition (*r* = -.19), suggesting an indirect effect of impulsivity through sleep disturbance. In summary, results demonstrated that higher impulsivity was related to more sleep disturbance and lower overall sleep quality in a euthymic BD sample, which, in turn, had significant deleterious effects on cognition. Overall, this was a methodologically strong study that was sufficiently powered, and it is the only study reviewed that attempted to parse causal relationships between sleep and impulsivity in BD. Limitations included use of self-reported sleep measures as opposed to objective sleep measures, lack of a healthy control group, and a cross-sectional study design, which ultimately prevents any causal conclusions.

The second study that examined the relationship between self-reported impulsivity and sleep/circadian rhythm disturbance was more limited methodologically. Dopierala and colleagues (2016) examined impulsivity and circadian rhythm disturbance in 54 patients with BD and 54 healthy controls who had no psychiatric history or first-degree relatives with psychiatric disorders. The impulsivity measure was the 10-item impulsive nonconformity subscale of the Short Oxford-Liverpool Inventory of Feelings and Experiences [O-LIFE, (O. Mason & Claridge, 2006), a self-report questionnaire proposed to measure facets of schizotypy. However, the 10-item impulsive nonconformity subscale is a valid self-report measure of impulsivity and includes items such as “Do you stop to think things over before doing anything?”, “Do you often have the urge to break or smash things?”, and “Do you often feel the impulse to spend money which you know you cannot afford?”. The circadian rhythm disturbance measure was the

Biological Rhythms Interview of Assessment in Neuropsychiatry [BRIAN (L. M. F. Giglio et al., 2009)], a 21-item interview measure designed to assess disturbance in five biological rhythm-related areas: sleep, activity, social activity, eating, and predominant rhythm (chronotype). The researchers calculated Spearman's rank correlation coefficients between the impulsive nonconformity subscale of the O-LIFE and the BRIAN subscales for the BD group and HC group separately. In the BD group, impulsive nonconformity was positively correlated with BRIAN activity disturbance subscale score (r_s = .31, medium effect size), eating disturbance subscale score (r_s = .36, medium effect size), chronotype subscale score (r_s = .43, medium to large effect size), and the total score (r_s = .38, medium effect size). In the HC group, only eating disturbance subscale score had a significant positive correlation with impulsive nonconformity (r_s = .31, medium effect size). This study had several significant limitations, most notably including a lack of statistical tests directly comparing the BD and HC groups on measures of interest (e.g., O-LIFE scores, BRIAN scores), which precludes the reader from knowing if impulsive non-conformity and rhythm disturbance are elevated in the BD group compared to the HC group. Other major limitations included no correction for multiple comparisons, not controlling for potentially important clinical covariates, and no explanation of diagnostic criteria for BD or of the instruments used to make the diagnoses. Minor limitations included the cross-sectional study design and absence of controlling for medication usage.

Two strong studies examined the association between behavioral impulsivity and sleep/circadian rhythm disturbance in BD. The first, a 2015 study by Volkert and colleagues, assessed the relationship between behavioral impulsivity and sleep disturbance in a sample of euthymic BD-I and BD-II outpatients (N = 70) and matched healthy controls (N = 70). Bipolar disorders were diagnosed according to *DSM-IV* criteria using structured clinical interviews, and healthy controls were screened using the structured Mini-International Neuropsychiatric Interview [MINI, (Sheehan et al., 1998)]. To assess for sleep disturbance, participants were asked if they had persistent sleep disturbances (middle or initial insomnia) in the month prior to the interview. The behavioral impulsivity measurement, completion time for incompatible trials of the Stroop Interference Test, was administered as part of a larger 90-min. neuropsychological testing battery. Independent t-tests and Chi-square analyses were used to test differences between the BD and HC groups – notably, there were no significant differences between BD and HC in behavioral impulsivity (Stroop incompatible) score (Cohen's d = .03, p = .395). Volkert et al. split the BD group into BD with cognitive deficits (N = 41) and BD without cognitive deficits (N = 29); participants were judged to have cognitive deficits if they performed 1.5 SD below the average of a normative data group on the full neuropsychological battery. T-tests and Chi-square tests revealed that the cognitive deficit subgroup had significantly higher scores on the "reduced sleep" item of a depression self-report questionnaire than the cognitively intact subgroup (t = 2.44, p =.017) and were more likely to endorse "initial/middle insomnia (y/n)" (χ^2 = 3.59, p = .049). Finally, the researchers used multiple linear regression to test clinical characteristics as predictors of cognitive scores, and found that history of a sleep disorder (b = .28, p = .029) and subthreshold depressive symptoms best predicted behavioral impulsivity as measured by Stroop Incompatible score (R^2 = .147). Overall, the findings in this study support chronic/recent sleep disturbances as predictors of behavioral impulsivity and other cognitive deficits in BD. The study had many methodological strengths, including extensive neuropsychological assessment of a large and well-characterized BD sample, an age and gender-matched control group, and detailed measurement of many clinical covariates. Limitations included the cross-sectional design and absence of a formal, well-validated measure of sleep disturbance.

The second study that examined behavioral impulsivity in relation to circadian rhythm disturbance in BD was conducted by Giglio and colleagues (2010). Participants included outpatients diagnosed with *DSM-IV* bipolar I disorder or bipolar II disorder (N = 81); diagnoses were confirmed using the SCID (M. B. Spitzer et al., 2002). Healthy control participants (N = 79) were also recruited from the hospital area and screened using the non-patient version of the SCID. To measure circadian and social rhythm disturbance, the BRIAN (described above) was administered (L. M. F. Giglio et al., 2009). A subset of the BD patients (n = 23) completed the Wisconsin Card Sorting Test (WCST) – percentage of perseverative errors was used as the measure of behavioral impulsivity (Berg, 1948). A Wilcoxon signed-rank test indicated that biological rhythm disturbance was significantly elevated in the BD group as compared to the HC group (p <.001). In the subset of BD participants who completed the WCST, multiple linear regression indicated that BRIAN disturbance score significantly predicted behavioral impulsivity (i.e., perseverative errors), controlling for depressive symptoms (b = .102, p < .001). The main limitation of this study was that only a small subset of BD patients completed the WCST, rendering their findings sensitive to chance. Similar to other studies reviewed, other limitations included the cross-sectional study design and the use of a self-report (interview-based) circadian rhythm disturbance measure.

Finally, three studies in our review measured risky/impulsive behavior and its relation to sleep/circadian rhythm disturbance in BD. A recent study by Keskin and colleagues (2018) explored the relationship between sleep disturbance and impulsivity-related clinical features (i.e., history of suicide attempts and impulse control disorders). Euthymic participants (N = 122) with SCID-diagnosed *DSM-IV* bipolar disorders were studied. Sleep disturbance measures were the PSQI, the ESS, and the General Sleep Questionnaire, a measure developed to evaluate general characteristics of sleep (Selcuk Aslan et al., 2006; Selçuk Aslan et al., 2005). The BD participants were divided into two groups, "poor sleepers" (PSQI score of ≥ 5) and "good sleepers" (PSQI score of < 5); t-tests, Mann Whitney U tests, and logistic regressions were run to compare clinical characteristics of the two groups. Results indicated that history of suicide attempt was more prevalent in the "poor sleepers" group, as was prevalence of current and lifetime impulse control disorder ($p = .045$ and $p = .028$ respectively). Limitations of this study include the lack of a control group, the cross-sectional study design, and absence of an objective sleep measurement. It also is worth noting that the measurements of impulsivity were not retrospective self-reports of behaviors. No formalized and validated measure of impulsivity was used, lessening the ability to draw strong conclusions about the explicit relationship between impulsivity and sleep disturbance.

A second study also examined history of suicide attempts and sleep disturbance in BD (Sylvia et al., 2012). Participants were diagnosed with *DSM-IV* bipolar I disorder, bipolar II disorder, cyclothymia, or bipolar disorder not otherwise specified with the aid of the MINI (Sheehan et al., 1998) diagnostic interview, and were confirmed to be euthymic by scores on mood symptom self-report questionnaires. Sleep disturbance was measured by item 4 of the Montgomery-Asberg Depression Rating Scale [MADRS, (Montgomery & Asberg, 1979)], a 10-item, clinician-administered assessment of depressive symptoms. The definition of "sleep disturbance" was a score of 2 or higher on this item. Impulsive behavior was operationalized as number of previous suicide attempts. Suicide attempts were more prevalent in the group that reported sleep disturbance (OR = 1.94, $p < .05$). Furthermore, the study used Cox proportional hazard regression to show that sleep disturbance is a precursor to bipolar mood episodes. This study included a large, well-characterized sample of BD participants, but a major limitation was that it lacked a validated, multi-item sleep disturbance measure, instead opting for a 1-item measure of "reduced sleep," which only encompasses one small facet of the sleep disturbance construct. The measure of impulsivity (number of past suicide attempts) was similarly limited in that it encompasses a very specific and relatively rare type of risky behavior that is not always impulsively driven.

The final study (Clements et al., 2015) employed a case-control study design to examine self-harm in BD versus non-BD patients. Participants were BD patients who had presented to an emergency care facility following an episode of self-harm (N = 103). Researchers used a nested case-control sample (N = 515) selected from individuals without a BD diagnosis who had presented to the same care facility following an episode of self-harm. BD diagnoses were made by the assessing emergency room clinician, based on current mental state and/or the patient's health records. Researchers defined self-harm as "any intentional self-poisoning or self-injury, irrespective of motivation." Sleep disturbance was measured by the clinician with one binary variable: "Sleep disturbance: yes or no." Researchers used univariate conditional logistic regression to test differences between the BD and the non-BD group on a number of clinical characteristics, including sleep disturbance. Sleep disturbance was more prevalent in the BD than non-BD group (OR = 1.737, p = .041). When sleep disturbance was entered into a multivariate logistic regression with other significant predictors of BD versus non-BD status, it was the most robust predictor of BD status (OR = 2.95, p =.011). This study had many significant limitations, including a non-specific, one-item, binary measure of sleep disturbance. The BD diagnosis was made by an emergency room clinician in a potentially high-stress, chaotic environment, and no distinction was made between bipolar mood states. Additionally, although suicide attempts and non-suicidal self-injury are often impulsive behaviors, this is not always the case; thus, the presence of “self-harm” is a potentially problematic measure of impulsivity. Nevertheless, the study indicated that sleep disturbance is more prevalent in BD self-harmers than non-BD self-harmers, suggesting a potential association between these characteristics that is specific to BD.

In summary, following an extensive systematic review of the literature, a scarcity of empirical research exists on the association between impulsivity and sleep/circadian rhythm disturbance in BD. We identified only seven studies that met inclusion criteria and directly examined the sleep/circadian rhythm disturbance and impulsivity relationship. There are major limitations to this body of research exceeding the mere fact that few studies have been conducted on the topic, including an overreliance on cross-sectional study designs and lack of valid measurements of important constructs. Thus, our discussion will seek to draw only tentative conclusions, opting instead for a stronger focus on discussion of current limitations and necessary directions for strengthening future research.

All seven studies included in our review demonstrate a positive relationship between sleep/circadian rhythm disturbance and heightened impulsivity (both self-reported and behavioral) in BD. Notably, these studies ranged substantially in their choice of impulsivity measure, so findings suggest that multiple facets of impulsivity may be related to sleep or circadian rhythm disturbance, although replication is imperative. Six of the seven studies in our review necessitated that BD participants were euthymic or in remission from mood episodes at the time of study; thus, evidence suggests that the association between sleep/circadian rhythm disturbance and heightened impulsivity is not merely an artifact of depressive or (hypo)manic episodes, but instead is present even during periods of remission. Although these findings are intriguing, conclusions must be qualified with numerous caveats and limitations, detailed below.

First, six of the seven eligible studies employed cross-sectional designs. Although one study employed path analysis, a more nuanced analysis method that can test hypotheses about causal connections between a set of variables, all data for the analysis were collected at the same timepoint, detracting from confidence in the predictive associations between variables. In three of the studies reviewed, it was clear that sleep/circadian rhythm disturbance preceded impulsivity based on measured timeframe of the variables, but predictive and/or casual connections cannot be assumed based on temporal precedence alone. Furthermore, cross-sectional studies relying on self-report data are plagued with recall and memory biases, given that human memory is fallible, state-dependent, and often selective (Sedgwick, 2014). Longitudinal and multi-wave research designs would critically enhance the ability to draw causal connections between impulsivity, sleep/circadian rhythm disturbance, and BD onset, symptom severity, and course. Ecological momentary assessment (EMA) studies would combat retrospective bias, maximize ecological validity, and allow for more granular examination of mechanisms and microprocesses (Shiffman, Stone, & Hufford, 2008). Finally, inasmuch as experimental research designs are feasible and ethical, their addition to this body of research would greatly enhance the ability to draw conclusions about mechanistic processes in BD.

Second, several studies evinced significant limitations in their measurements of sleep disturbance. Often, the sleep disturbance construct was captured with administration of one or two yes/no items; alternately, a single item related to sleep disturbance was taken from a multi-item depressive symptom self-report questionnaire. Future research should strive to utilize multi-item, standardized, well-validated, and reliable self-report measurements of sleep disturbance, given that it is a multi-faceted construct and it is valuable to capture maximal construct variance.

Third, all studies discussed in our review relied solely on self-reported or interview measurements of sleep/circadian rhythm disturbance; none utilized objective or physiological measurement methods. Given the aforementioned methodological concerns with reliance on self-report measures (e.g., recall bias), and given findings that subjective and objective measures of sleep parameters rarely have high concurrence and agreement (Harvey & Tang, 2012; Lauderdale, Knutson, Yan, Liu, & Rathouz, 2008), it is vital that future research diversify its methodology and include measurements such as actigraphy, polysomnography, dim light melatonin onset, and peak skin temperature measurements to capture objective sleep and circadian parameters. Additionally, sleep parameters ought to be studied with more specificity and parsed into more precise subcomponents (e.g., sleep duration, sleep timing, latency of sleep onset, fragmentation of sleep period, and time spent in specific sleep stages) in order to improve understanding of disturbance as it relates specifically to BD. Sleep homeostatic processes and circadian processes are controlled by different neurobiological mechanisms, and although it is difficult to isolate these processes in humans, future research should attempt to better separate contributions from these processes in BD, and physiological measurements would aid in their demarcation and elucidation.

Fourth, there is a scarcity of research examining sleep and circadian rhythm disturbance as it relates to specific types of impulsive behaviors in BD (e.g., substance use, gambling, aggression, and risky sexual behavior). The three studies that examined real-life impulsive behaviors focused on self-harm (suicide attempts and other medically serious self-harm incidents), which is a specific type of risky behavior that is associated with negative urgency but is not always undertaken impulsively. To our knowledge, no validated and widely used measure of impulsive, risky behavior exists currently, and development of such a measure would facilitate a more nuanced understanding of how specific impulsive behaviors in BD relate to sleep and circadian rhythm disturbance.

Fifth, all studies reviewed except one elected to measure only one facet of impulsivity using one method (e.g., self-report or behavioral or real-world impulsive behavior). It is beneficial that researchers have attempted to examine different aspects of this multi-layered construct, but future research should strive to incorporate measurements of different facets of impulsivity in the same study and using the same sample, so as to facilitate more direct comparison of subtypes of impulsivity and their relations to sleep/circadian rhythm disturbance. Both self-report and behavioral measures of impulsivity could be used in a multiple regression framework as related, but contributing unique variance to predictive models in BD.

Sixth, no studies reviewed made an effort to account for or control for the effects of medication on sleep or circadian disturbance in BD. Medications, psychotropic or otherwise, have a well-documented and substantial effect on sleep (DeMartinis & Winokur, 2007); often, it is hard to parse whether sleep changes are an effect of medication or an effect of the illness. Given the ethical and practical difficulties of studying unmedicated BD patients, researchers should take care to carefully record medication status and to statistically control for the effects. Even with careful measurement and statistical control, there is no way to fully resolve this confound, but researchers should strive to remain aware of it while designing, implementing, and interpreting studies on sleep and BD.

Finally, given the research reviewed earlier suggesting a strong relationship between sleep/circadian rhythm disturbance and impulsivity in healthy controls, future research should seek to understand the role of interaction between these two variables in possibly exacerbating BD symptom severity, time to relapse, frequency or severity of episodes, and functional impairment. It is possible, given the ubiquity of impulsivity and sleep/circadian disturbance in BD, that these two factors have a pernicious and synergistic effect over and above the influence of either one alone. Future studies should test this theory by employing carefully selected, hypothesis-driven research designs, state-of-the-art statistical analyses, and focus on elucidating behavioral and neurobiological mechanisms of sleep/circadian rhythm disturbance and impulsivity in BD.

Proposed Theoretical Integration and Conclusion

Our systematic review of the literature has demonstrated early evidence for bidirectional associations between impulsivity and sleep/circadian rhythm disturbance in BD that persist even during euthymic phases of the illness. In furtherance of gaining more comprehensive understanding of BD, it will be necessary to better understand the mechanisms that link impulsivity, sleep/circadian rhythm disturbance, and BD rather than continuing to demonstrate mere associations. To this end, we made recommendations for future research directions that allow for examination of mechanisms in the section above; this final section of our review focuses on exploring and synthesizing theories in an attempt to situate sleep/circadian rhythm disturbance and impulsivity into an overarching framework of BD etiology and course.

As yet, mechanisms underlying the association between mood dysregulation, impulsivity, and sleep/circadian rhythm disturbance are not well understood or tested. However, some researchers have suggested possible mechanisms and theoretical associations for these dimensions. In a comprehensive review, Harvey (2008) suggested that there may be a pernicious, escalating, bidirectional effect of sleep/circadian rhythm disturbance at night and increasing impulsivity during the day, resulting in increased mood dysregulation. It is possible that impulsivity is an indirect pathway through which sleep/circadian rhythm disruption may trigger affective dysregulation. Alternatively, deficits in ability to inhibit and regulate behavior observed in BD could be moderated by sleep/circadian rhythm disturbance, given that research in healthy individuals demonstrates interindividual variability in sensitivity to sleep disruption (Chuah et al., 2006). Another possibility is that individuals with BD demonstrate trait-like abnormalities in circadian rhythms (e.g., high eveningness) that predispose stronger reaction to environmental sleep/circadian rhythm perturbances. In turn, external sleep/circadian rhythm perturbation may lead to decreased top-town control (e.g., response inhibition), which triggers affective disturbance. All of these pathways are possible, but none have been tested empirically, and improved methodology and study design could enable researchers to empirically test these and other conceivable mechanisms.

In a neuroimaging review, McKenna and Eyler (2012) drew attention to the crucial role of the prefrontal cortex (PFC) in understanding the neural correlates of sleep/circadian disturbance, cognitive deficits (including decreased response inhibition), and BD. The PFC is a complex and multi-faceted brain area that is critically important for regulating and modulating midbrain inputs related to processes such as emotion and reward (Teffer & Semendeferi, 2012). McKenna and Eyler synthesized research demonstrating that sleep/circadian disturbance compromises the functional integrity of the PFC and increases behavioral impulsivity in healthy adults. They made the argument that the PFC is particularly sensitive to sleep/circadian rhythm disruption. They also summarized evidence (as we do above) that BD is linked with pervasive PFC deficits. Thus, they contended that the PFC is a brain area where sleep/circadian rhythm disturbance, inhibition, and BD are likely to interact on a neural level. They speculated that sleep/circadian rhythm disturbance may decrease the ability of the PFC to exert top-down control on limbic, midbrain activation, leading to increased mood dysregulation.

McKenna, Drummond, and Eyler (2014) provided the first neuroimaging evidence for circadian/sleep disturbance affecting PFC activation in euthymic BD. They compared a BD group with a healthy control group on a number of objectively measured parameters of sleep/circadian disturbance (e.g., actigraphic sleep onset latency and activity rhythm amplitude) and found that the BD group showed significant disturbance on a number of sleep-related dimensions compared to healthy controls. They found that abnormal sleep efficiency and rhythm robustness were, in turn, linked to decreased PFC activation during a working memory task in the MRI scanner. This is evidence for the theory that sleep and circadian disturbance are directly associated with decreased PFC integrity. Given that deficit in dorsolateral PFC (dlPFC) activity is the strongest neural correlate of behavioral impulsivity and inhibition (Moeller et al., 2014), we agree with their assertion that the PFC plays a central role in the intersection between sleep/circadian rhythm disturbance, inhibition, and BD.

Another similar and relevant neural theory of BD proposes that abnormal PFC modulation of subcortical and medial temporal brain areas results in mood dysregulation (Strakowski, Adler, Holland, Mills, & DelBello, 2004). We propose the following integration of impulsivity into this framework: if impulsivity is conceptualized as “the tendency to act without forethought or reflection,” then we suggest that this tendency may be driven by both 1) an inability for top-down control to inhibit a pre-potent response, and also 2) increased bottom-up urgency to act, fueled by emotion-driven or reward-driven neural circuitry. Thus, one facet of impulsivity (e.g., response inhibition) is a top-down process modulated by the PFC, and another facet (e.g., trait impulsivity, delay discounting) is a reward- or emotion-driven process modulated by subcortical and medial temporal areas. The combination of these facets of impulsivity may lead to heightened vulnerability to emotion dysregulation, and it is possible that sleep/circadian rhythm disturbance increase this vulnerability. To test this idea, we re-emphasize the importance of examining different facets of impulsivity within the same model and sample. One neuroimaging study in partial support of our theory compared dlPFC and ventral striatum inputs to the ventrolateral PFC (vlPFC) in BD versus HC during a roulette task that had both "safe" and "risky" rewards (L. Mason, O'Sullivan, Montaldi, Bentall, & El-Deredy, 2014). BD patients showed more input from "bottom-up" areas (i.e., the ventral striatum) during anticipation and outcome phases of the task, whereas HC showed input from both the "top-down" dlPFC and "bottom-up" ventral striatum. Moreover, trait impulsivity in the BD group was inversely associated with dlPFC activation during "safe" reward trials. These findings suggest that trait impulsivity in BD may contribute to the tendency to overvalue limbic/reward input and undervalue dlPFC input.

McKenna and Eyler (2012) made a good case for how sleep/circadian rhythm disturbance may facilitate increased impulsivity and/or disinhibition, subsequently leading to mood dysregulation. We would like to add that impulsive behaviors in BD also may lead to sleep/circadian rhythm disturbance. Mansell and colleagues (2007) outlined a cognitive behavioral model of BD and described the role of "ascent behaviors" in maintaining or escalating mood symptoms. They defined ascent behaviors as "behavioral strategies" that serve to increase levels of activation (e.g., seeking social stimulation). We posit that impulsive or risk-taking behaviors compose a subset of "ascent behaviors" that escalate an individual towards mania. Often, impulsive or risky behaviors such as drinking, self-harming, or gambling can have serious negative consequences and can increase life stress and chaos. Thus, it is feasible to propose that impulsive or risky behaviors could lead to sleep/circadian rhythm disturbance due to their ability to disrupt regular social rhythms/activity schedules. Sleep/circadian rhythm disturbance, in turn, have been shown to trigger mood episodes. Hence, it is reasonable to theorize that impulsivity and sleep/circadian rhythm disturbance could have interactive and bidirectional effects on one another in BD.

Why continue to study the relationship between sleep/circadian rhythm disturbance and impulsivity in BD? Separately or together, these features could function as crucial mechanisms that interact to contribute to onset and/or maintenance of BD. Even if they do not have mechanistic relationships to BD onset or course, they are important core features that remain present during euthymia and contribute to continued interepisode functional impairment and morbidity. Research in healthy individuals demonstrates that they have interactive effects, so it is reasonable to assume that they also will intermingle in BD. Further study could help to improve early intervention, prevent episode recurrence, and generally improve treatment targets in a disorder that often remains resistant to existing treatments and interventions.

Table 8. *List of studies included in the systematic review*

Authors	Year	Sample description	N (% BD)	% Female	Clinical diagnosis tool	Study Design	Measure of Impulsivity	Measure of Sleep/Circadian Rhythm
Clements et al.	2015	Self-harmers who presented to an emergency care facility following self-harm	618 (17%)	57%	Assessing ER clinician based on current mental state and past medical records	Case-control	"Any intentional self-poisoning or self-injury, irrespective of motivation"	One clinician evaluated item: "Sleep disturbance: yes or no."
Dopierala et al.	2016	Outpatients with euthymic BD and matched control subjects	108 (50%)	70%	Not reported	Cross-sectional	Impulsive non-conformity scale of the O-LIFE	Biological rhythms; BRIAN
Giglio et al.	2010	Patients with euthymic BD and healthy control subjects	160 (51%)	72%	SCID	Cross-sectional	Wisconsin Card Sorting Test: perseverative errors	Biological rhythms; BRIAN

Keskin et al.	2018	Outpatients with euthymic BD	122 (100%)	64%	SCID	Cross-sectional	History of suicide attempts and prevalence/incidence of impulse control disorders	General Sleep Questionnaire; PSQI
Russo et al.	2015	Outpatients with euthymic BD	117 (100%)	59%	SCID	Cross-sectional	Barratt Impulsivity Scale	Epworth Sleepiness Scale; PSQI
Sylvia et al.	2012	Euthymic BD	483 (100%)	64%	SCID	Cross-sectional	Number of previous suicide attempts	Score of 2 or higher on 'reduced sleep' item of the MADRS (item 4)
Volkert et al.	2015	Outpatients with euthymic BD and matched healthy controls	140 (50%)	56%	DSM-IV diagnosis by clinical interview	Cross-sectional	Stroop Color-Word Test, completion time for interference conditions	Patients were asked if they had sleep disturbance (initial or middle insomnia) in the four weeks preceding the interview

SCID = Structured Clinical Interview for the DSM-IV; BRIAN = Biological Rhythms Interview of Assessment in Neuropsychiatry; O-LIFE = Oxford-Liverpool Inventory of Feelings and Experiences; MADRS = Montgomery-Asberg Depression Rating Scale

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