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Restless Pillow, Ruffled Mind: Sleep and Affect Coupling in Interepisode Bipolar Disorder

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Abstract

Disturbances in sleep and affect are prominent features of bipolar disorder, even during interepisode periods. Few longitudinal studies have prospectively examined the relationship between naturally occurring sleep and affect, and no studies to date have done so during interepisode periods of bipolar disorder and using the entire set of “gold standard” sleep parameters. Participants diagnosed with bipolar I disorder who were interepisode ($n = 32$) and healthy controls ($n = 36$) completed diagnostic and symptom severity interviews, and a daily sleep and affect diary, as well as an actigraphy sleep assessment, for eight weeks ($M = 54$ days, ± 8 days). Mutual information analysis was used to assess the degree of statistical dependence, or coupling, between time series data of sleep and affect. As measured by actigraphy, longer sleep onset latency was coupled with higher negative affect more strongly in the bipolar group than in the control group. As measured by sleep diary, longer wakefulness after sleep onset and lower sleep efficiency were coupled with higher negative affect significantly more strongly in the bipolar group than in the control group. By contrast, there were no significant differences between groups in the degree of coupling between any measures of sleep and positive affect. Findings support the coupling of sleep disturbance and negative affect during interepisode bipolar disorder. Ongoing monitoring of sleep-affect coupling may provide an important target for intervention in bipolar disorder.

Keywords

bipolar disorder; sleep; mood; ecological momentary assessment

Bipolar disorder is a severe psychiatric illness that affects approximately 2% to 4% of the U.S. population (Merikangas et al., 2007) and is ranked among the top 10 leading causes of disability worldwide (World Health Organization, 2001). Despite advances in the treatment of bipolar disorder recurrence rates remain high (Gitlin, Swendsen, Heller, & Hammen, 1995), and a significant proportion of bipolar patients continue to be symptomatic and functionally impaired between episodes of illness (Altshuler et al., 2006; Joffe, MacQueen, Marriott, & Young, 2004; Vieta, Sánchez-Moreno, Lahuerta, & Zaragoza, 2008). The persistence of interepisode symptoms and impairment are of great concern because these reduce patients' quality of life and interfere with recovery (Gitlin, Mintz, Sokolski, Hammen, & Altshuler, 2011; Judd et al., 2008). To date, the interepisode period has received minimal research attention. By shifting the focus of study to this period it may be possible to identify the factors that sustain impairment outside of acute episodes and maintain vulnerability to triggers of relapse. This study focuses on two such factors: sleep and affective functioning.

Disturbed sleep is a core feature of clinical episodes in bipolar disorder (*DSM-IV-TR*; American Psychiatric Association, 2000). Several short-term prospective studies document the persistence of sleep difficulties between episodes of bipolar disorder. Interepisode bipolar participants report longer sleep onset latencies on daily sleep diaries relative to control participants (Harvey, Schmidt, Scarna, Semler, & Goodwin, 2005; Millar, Espie, & Scott, 2004) and exhibit more variability in actigraphy-measured sleep and wake durations relative to controls (Millar et al., 2004). Another study employing actigraphy found no significant group differences in sleep onset latency, sleep duration, or wake duration. Instead, this study found a more fragmented sleep/wake rhythm and less day-to-day stability among interepisode bipolar participants relative to controls (Jones, Hare, & Evershed, 2005). In a related line of research, participants assessed to be at risk for bipolar spectrum disorders based on scores on a hypomanic temperament scale (Meyer & Maier, 2006) and those diagnosed with bipolar spectrum disorders (Shen, Alloy, Abramson, & Sylvia, 2008) exhibited less regularity in social rhythms, or daily routines that help entrain natural circadian rhythms and the sleep-wake cycle. Reduced social rhythm regularity, in turn, predicted faster relapse among bipolar spectrum participants (Shen et al., 2008). These findings are consistent with social *zeitgeber* theory (Ehlers, Frank, & Kupfer, 1988; Frank, Swartz, & Kupfer, 2000), which posits that individuals with bipolar disorder have a biological vulnerability in the internal clock that regulates circadian rhythms and the sleep-wake cycle. Disruptions in social rhythms are thought to trigger this vulnerability, leading to disturbances in sleep and, ultimately, episode relapse (Frank et al., 2000; Grandin, Alloy, & Abramson, 2006).

Taken together, the accruing evidence suggests that the sleep and social rhythms of bipolar participants, or those at risk for bipolar disorder, are substantially disturbed. Furthermore, the evidence suggests that disturbances in sleep and social rhythms persist outside of acute mood episodes and may play a causal role in the onset of new episodes. However, there is no agreement on the precise aspects of sleep affected. For example, we do not yet know whether subjective, objective, or both types of sleep are disturbed, nor the sleep parameters that are most disturbed, during interepisode periods of bipolar disorder. More comprehensive assessments of interepisode sleep in bipolar samples are needed to address these gaps in knowledge.

A significant disturbance in mood is a defining feature of depressive, manic, hypomanic, and mixed episodes in bipolar disorder (*DSM-IV-TR*; American Psychiatric Association, 2000). Affective disturbances also persist between episodes of bipolar disorder. Studies using ecological momentary assessment methods conducted over the course of one to four weeks document higher levels of negative affect (Havermans, Nicolson, Berkhof, &

deVries, 2010; Lovejoy & Steuerwald, 1995, but see Knowles et al., 2007 for nonreplication) and more variability in negative affect (Hofmann & Meyer, 2006; Knowles et al., 2007; Lovejoy & Steuerwald, 1995) among subsyndromal bipolar samples relative to controls. Findings with regard to positive affect, however, are less clear. Increased variability in positive affect has been consistently found among subsyndromal bipolar samples relative to controls (Hofmann & Meyer, 2006; Knowles et al., 2007; Lovejoy & Steuerwald, 1995), but support for differences from controls in mean levels of positive affect is inconsistent (Havermans et al., 2010; Hofmann & Meyer, 2006, but see Knowles et al., 2007 and Lovejoy & Steuerwald, 1995 for nonreplications). Overall, the evidence suggests that affective functioning is substantially disturbed between episodes of bipolar disorder, with more consistent findings for dysregulation in negative than positive affect.

Disturbances in sleep and affect may be linked and, possibly, mutually maintaining (Harvey, 2008; Wehr, 1990). Indeed, sleep disturbance is a key predictor of mood symptoms. It is one of the most commonly reported prodromes of mania and depression (Jackson, Cavanagh, & Scott, 2003). In prospective studies with bipolar patients, sleep loss has been correlated with daily manic symptoms (Barbini, Bertelli, Colombo, Smeraldi, 1996) and with depressive symptoms at a 6-month follow-up (Perlman, Johnson, & Mellman, 2006). Self-reported changes in sleep duration have also been prospectively linked to self-reported changes in mood (measured using a single scale ranging from depressed to manic) in bipolar participants (Bauer et al., 2006). Thus, studies suggest that a disturbance in sleep can adversely impact mood. Conversely, a happy mood induced before bedtime has been associated with sleep difficulties among interepisode bipolar participants relative to controls (Talbot, Hairston, Eidelman, Gruber, & Harvey, 2009). To summarize, disturbances in sleep and mood may be bidirectionally related in bipolar disorder (Harvey, 2008; Wehr, 1990).

Taken together, despite the strength of the existing findings, several issues remain unresolved. Few studies have assessed interepisode sleep comprehensively, using the entire set of the “gold standard” sleep parameters collected by both subjective and objective measures, as is recommended by established guidelines (Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006), and no study to date has done so for durations longer than one week. Given substantial night-to-night variability in sleep, particularly among sleep disturbed samples, three to five weeks of daily sleep monitoring are necessary to achieve stable, representative, and reproducible estimates for key sleep parameters (Wolgemuth, Edinger, Fins, & Sullivan, 1999). Relatively short periods of observation also limit our knowledge of interepisode affect, potentially accounting for inconsistent findings with regard to positive affect. Finally, while disturbances in sleep (e.g., Barbini et al., 1996; Perlman et al., 2006) and affect (e.g., Henry et al., 2008) appear to be critical processes in maintaining pathology in bipolar disorder, their roles have been examined largely independently. Preliminary findings suggest that a laboratory-induced mood can adversely impact sleep in interepisode bipolar participants (Talbot et al., 2009). However, only one study has examined the relationship between naturally occurring affect and sleep in interepisode bipolar participants; the findings supported a bidirectional relationship between negative affect and wake time in bipolar relative to control participants (Talbot et al., in press). However, this study focused on a single sleep parameter (self-reported wake time) and was limited to one week of observation.

To further clarify this important domain, the aim of the present study was to prospectively examine sleep, affect, and their potential relationship, or coupling, in interepisode bipolar disorder. Our study is the first to test this relationship by employing the most advanced methodology to date. We assessed distinct aspects of sleep using all standard sleep parameters measured via diary and actigraphy (Buysse et al., 2006). We measured both positive and negative affect. Moreover, we used daily sampling collected over the course of

eight weeks. The study was designed to test three hypotheses. First, based on previous findings of pervasive sleep problems in bipolar patients during nonacute periods of illness (e.g., Harvey et al., 2005), we predicted that the bipolar group would exhibit greater sleep disturbance than the control group. Second, based on previous findings documenting pervasive affective disturbance during nonacute periods of illness (e.g., Hofmann & Meyer, 2006; Lovejoy & Steuerwald, 1995) we predicted that the bipolar group would exhibit greater affective disturbance than controls. Finally, based on previous findings suggesting sleep and affect may be closely interlinked during nonacute periods of bipolar disorder (e.g., Talbot et al., in press), we predicted greater sleep-affect coupling in the bipolar group relative to controls.

Method

Participants

Participants were 32 adults, ages 18 – 64, diagnosed with bipolar disorder Type I, who were currently interepisode, and 36 healthy adults with no history of Axis I psychiatric disorders or sleep disorders. Participants were recruited from the San Francisco Bay Area through online advertisements and flyers posted in the community. Participants who contacted the lab were initially screened for their likelihood of meeting the study's eligibility criteria (described below) with a phone interview. This screening interview included an abbreviated version of the Structured Clinical Interview for DSM (SCID; First, Spitzer, Gibbon, & Williams, 2007) with additional probes from the mood module. Potential participants were also asked about: (a) current medical conditions; (b) current sleep problems; (c) substance or alcohol use in the preceding 6 months; and (d) homelessness status.

All participants were required to meet the following criteria: (a) no evidence of a medical condition that may account for sleep disturbance, such as severe head injury, a neurological disease (e.g., Alzheimer's disease), or an autoimmune disorder (e.g., HIV); (b) no evidence of a confounding sleep disorder such as sleep apnea, periodic limb movement disorder, a moderate or severe parasomnia, or a circadian rhythm disorder (diagnoses confirmed at baseline visit by the Duke Structured Interview for Sleep Disorders; DSISD; Edinger et al., 2004); (c) no evidence of alcohol or substance abuse or dependence in the past 6 months (confirmed at baseline visit by the SCID); and (d) a stable living arrangement.

Inclusion in the bipolar group required that participants: (a) meet diagnostic criteria for bipolar disorder Type I according the SCID (First et al., 2007); and (b) exhibit interepisode status throughout the study. Interepisode status was defined by the absence of a depressive or (hypo)manic episode in the preceding month (as assessed by the SCID) and scoring at asymptomatic to mild symptom levels on the Clinician Rated Inventory of Depressive Symptomatology (IDS-C; score ≤ 23 ; Rush, Gullion, Basco, Jarrett, & Trivedi, 1996) and the Young Mania Rating Scale (YMRS; score ≤ 11 ; Young, Biggs, Ziegler, & Meyer, 1978) at each study visit; (c) be in the care of a psychiatrist. Participants who met criteria for a current (past month) mood episode and/or exceeded symptom severity thresholds were excluded from further evaluation, and were assessed for safety, provided monetary compensation for their time, and (with permission) recontacted in 2 weeks for reassessment.

The median age of illness onset for the bipolar group was 16.0 years (interquartile range = 6.8). Bipolar participants reported a median of 4.0 manic or hypomanic episodes (IQR = 11.0) and 4.0 depressive episodes (IQR = 12.0) over the course of their lifetimes. Twenty of 32 (62.5%) bipolar participants reported a psychiatric hospitalization, with a median of 1.0 previous hospitalizations (IQR = 2.8). Given that bipolar disorder is typically comorbid with other psychiatric disorders (Kessler, Chiu, Demler, & Walter, 2005), participants in the bipolar group were not excluded on the basis of currently comorbid psychiatric diagnoses

other than alcohol or substance abuse or dependence in the previous 6 months. However, inclusion in the bipolar group required that bipolar disorder be the primary diagnosis (Di Nardo, Moras, Barlow, Rapee, & Brown, 1993). Eleven of 32 bipolar participants (34.4%) had at least one currently comorbid Axis I disorder diagnosis. Current comorbid diagnoses included specific phobia ($n = 6$), generalized anxiety disorder ($n = 4$), social phobia ($n = 3$), panic disorder ($n = 2$), binge eating disorder ($n = 2$), and posttraumatic stress disorder ($n = 1$).

On the basis that a medication-free group would be unfeasible and unrepresentative, participants were not excluded from the bipolar group if they were receiving medications prescribed for bipolar disorder. All but two participants in the bipolar group ($n = 30$) were being treated with pharmacological agents; 50.0% ($n = 15$) were taking antidepressants, 43.3% ($n = 13$) lamotrigine, 16.7% ($n = 5$) lithium, and 10.0% ($n = 3$) valproic acid. In addition, 20.0% ($n = 6$) were taking hypnotics (i.e., benzodiazepine, zolpidem). Nineteen of 32 (59.4%) bipolar participants were being treated with more than one medication. No control participants were taking psychotropic medications.

Inclusion in the control group required that participants: (a) show no evidence of current or lifetime Axis I psychiatric disorders based on the SCID (First et al., 2007); and (b) score within the asymptomatic to mild symptom severity range on the IDS-C (score ≤ 23 ; Rush et al., 1996) and the YMRS (score ≤ 11 ; Young et al., 1978). Control participants were also required to show evidence of normal sleep. Normal sleep was defined as: (a) the absence of any diagnosable sleep disorder (including insomnia) based on the DSISD (Edinger et al., 2004); and (b) scoring below established cutoffs for sleep disturbance on the Insomnia Severity Index (ISI; score ≤ 7 ; Bastien, Vallieres, & Morin, 2001) and the Pittsburgh Sleep Quality Index (PSQI; score ≤ 5 ; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989).

Measures

Psychiatric and sleep disorders—The Structured Clinical Interview for *DSM-IV* (SCID; First et al., 2007) and the Duke Structured Interview for Sleep Disorders (DSISD; Edinger et al., 2004) were used to assess psychiatric and sleep disorder history. The SCID has been shown to have strong interrater reliability (Williams et al., 1992). In the current study, diagnostic interrater reliability was established for a randomly selected sample of audio taped interviews ($n = 17$). Primary diagnoses (bipolar or control) matched those made by the original interviewer in all cases ($k = 1.00$). The DSISD is a semistructured interview designed to ascertain Research Diagnostic Criteria defined sleep disorder diagnoses (Edinger et al., 2004), as well as sleep disorders within both the *DSM-IV-TR* (American Psychiatric Association, 2000) and the International Classification of Sleep Disorders (American Sleep Disorders Association, 1997) nosologies. The DSISD has been shown to have good reliability and validity (Edinger et al., 2009).

Mood symptom severity—The Clinician Rated Inventory of Depressive Symptomatology-Clinician Rated (IDS-C; Rush et al., 1996) and the Young Mania Rating Scale (YMRS; Young et al., 1978) were used to assess current mood symptoms. The IDS-C is a 30-item interview measure of depression symptom severity. Scores range from 0 to 84, with higher scores indicating greater symptom severity. Scores less than 24 indicate asymptomatic to mild symptom severity (Rush et al., 1996). The IDS-C has demonstrated good psychometric properties (Rush et al., 1996). The YMRS is an 11-item interview measure of mania symptom severity. Scores range from 0 to 60, with higher scores indicating greater symptom severity. Scores less than 12 indicate asymptomatic to mild symptom severity (e.g., Suppes et al., 2005). The YMRS has demonstrated good psychometric properties (Young et al., 1978). Intraclass correlations (Shrout & Fleiss, 1979)

between the original interviewer and an independent rater for a randomly chosen subset of study participants ($n = 42$) were strong for the IDS-C ($r = .90$) and YMRS ($r = .84$).

Sleep symptom severity—The Insomnia Severity Index (ISI; Bastien et al., 2001) and the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) were used to assess current severity of insomnia and sleep disturbance, respectively. The ISI is a 5-item self-report scale. Scores range from 0 to 28, with higher scores indicating greater insomnia severity. A score greater than 7 identifies clinically significant insomnia (Bastien et al., 2001). The ISI has demonstrated good internal reliability and is sensitive to change (Bastien et al., 2001). The PSQI consists of 19 self-rated questions and five questions rated by a bed partner or roommate (if one is available). The self-rated questions yield seven “component” scores that measure subjective sleep quality, sleep onset latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, and daytime functioning. The seven component scores are summed to provide a global score ranging from 0 to 21, with higher scores indicating greater sleep disturbance. A score greater than 5 identifies a clinically significant sleep disturbance with high sensitivity and specificity (Buysse et al., 1989). The PSQI has demonstrated good internal consistency and test–retest reliability (Carpenter & Andrykowski, 1998).

Medication treatment—Medication treatment was quantified using the Somatotherapy Index (Bauer et al., 1997). This index is adapted from the scale used in the National Institute of Mental Health Collaborative Study on the Psychobiology of Depression (Mueller et al., 1999) specifically for use with bipolar disorder patients. Participants provided names, dosages, and frequency and duration of use for each currently prescribed medication. Specific ratings were made to evaluate lithium, antidepressant, valproic acid, carbamazepine, and alternative (e.g., lamotrigine) treatment levels. These ratings were made on a 0–4 scale, with higher scores indicating higher treatment levels. Blood serum levels are needed to rate mood stabilizer levels higher than a “1.” As this information was unavailable, we rated mood stabilizer levels as either 0 (*treatment is absent*) or 1 (*treatment is present*). A total Somatotherapy Index score was then calculated for each participant on a 6-point scale (0–5) (Bauer et al., 1997). The Somatotherapy Index is similar to the medication quantification method recommended by Phillips and colleagues (e.g., Almeida, Versace, Hassel, Kupfer, & Phillips, 2010) in reflecting both the dose and variety of medications taken. The Somatotherapy Index is reliable and has been used in bipolar samples (e.g., Johnson et al., 2008; Perlman et al., 2006; Sajatovic, Bauer, Kilbourne, Vertrees, & Williford, 2006).

Daily sleep—Based on the recommendations for sleep research (Buysse et al., 2006) standard sleep variables (outlined below) were calculated using both actigraphy and sleep diary. Actigraphs (Mini Mitter AW64 Actiwatchs, Respironics Inc.) are small devices, worn like wristwatches and used to assess sleep using motion detection. Embedded within each device are a miniaturized piezoelectric acceleration sensor, a processor, and memory. The device detects information about physical motion and translates it to numerical data. The frequency of motions is summarized into epochs of specified time duration (we sampled at 1-min epochs) and stored in memory. These data were downloaded to a computer using Respironics Actiware Version 5.5 (Respironics, Inc.) and the following sleep parameters were calculated: *sleep onset latency*, the time between bedtime and sleep onset; *wake after sleep onset*, the time awake during the night between sleep onset and the final awakening; *terminal wakefulness*, the time awake between the final awakening and the final arising; *total wake time*, sleep onset latency + wake after sleep onset + terminal wakefulness (e.g., Morin, Kowatch, & Wade, 1989); *time in bed*, the time between bedtime and the final arising; *total sleep time*, the time between sleep onset and the final awakening; *number of*

awakenings, the number of times the participant wakes up between sleep onset and the final awakening; and *sleep efficiency*, the proportion of time asleep while in bed. Nights when participants indicated removing their watches were excluded from analysis. Sleep assessed via actigraphy is moderately to strongly (.63–.90) correlated with sleep assessed via polysomnography in normal sleepers (e.g., Cole, Kripke, Gruen, Mullaney, & Gillin, 1992). Actigraphy has been validated in clinical samples (Sadeh, Hauri, Kripke, & Laurie, 1995) and has been successfully employed with bipolar patients (e.g., Harvey et al., 2005; Jones, Hare, & Ever-shed, 2005; Millar et al., 2004). Actigraphy is ideal for the naturalistic assessment of sleep as it is nonintrusive and capable of storing large amounts of continuously collected data. A sleep diary was designed to yield the same sleep parameters as measured by actigraphy, namely: *sleep onset latency*, *wake after sleep onset*, *terminal wakefulness*, *total wake time*, *time in bed*, *total sleep time*, *number of awakenings*, and *sleep efficiency*. The sleep diary has been shown to be reliable (Morin & Espie, 2003) and is the recommended subjective measure of sleep (Buysse et al., 2006).

Daily affect—Self-reported positive affect (PA) and negative affect (NA) were measured using the Positive and Negative Affect Scale (PANAS; Watson, Clark, & Carey, 1988). The PANAS consists of 10 positive adjectives (attentive, interested, alert, excited, enthusiastic, inspired, proud, determined, strong, active) and 10 negative adjectives (distressed, upset, hostile, irritable, scared, afraid, ashamed, guilty, nervous, jittery). Each adjective is rated on a 5-point scale (1 = *very slightly or not at all* and 5 = *extremely*). This measure has good psychometric properties, and has been used extensively in mood research (Watson, Clark, & Carey, 1988) including studies with bipolar samples (e.g., Hofmann & Meyer, 2006; Knowles et al., 2007; Lovejoy & Steuerwald, 1995).

Procedure

The University of California's Committee for the Protection of Human Subjects approved all study procedures. After providing informed consent, participants completed a demographic questionnaire, and were interviewed using the SCID, the DSISD, the IDS-C and the YMRS. Trained psychology doctoral students or a postdoctoral fellow administered all interviews. The ISI and PSQI were administered to assess for potential insomnia or sleep disturbance. Names, dosages, frequency, and duration of use for each currently prescribed medication were recorded. Eligible participants were given an actigraph and asked to wear it continuously for 4 weeks, until their second lab visit. Participants were also provided 4 weeks of daily sleep and affect diaries (to return by mail or at next lab visit). Participants were instructed to complete the sleep diary each morning immediately upon awakening and the affect diary each evening before bedtime. Participants were asked to call a voice mailbox after completion of each diary (morning and evening), in order to obtain a time-stamped record of completion. Participants completed a sample page with the experimenter to ensure that they understood each diary item.

Participants returned for a second lab visit 4 weeks following their initial visit. During this visit, the SCID mood module, the IDS-C, and YMRS were readministered to confirm continued interepisode status. Participants eligible to continue were administered the ISI and PSQI. Actigraphy data collected since the first laboratory visit were downloaded and the actigraph was reinitialized. Participants were asked to wear the actigraph continuously for another 4 weeks until their third lab visit. Participants were again provided 4 weeks of daily sleep and affect diaries. Participants returned to the lab for a third (and final) visit 4 weeks following the second lab visit. During this visit, the same procedure as described for the second visit was followed. Participants were compensated for their participation.

Statistical Analysis

Preliminary analyses were conducted to examine group differences on demographic variables (age, gender, ethnicity, marital status, annual household income, employment status), clinician-rated symptom severity scales (IDS-C and YMRS) and self-reported sleep disturbance questionnaires (ISI and PSQI). Mann–Whitney *U* tests were used for continuous variables and chi-square tests were used for categorical variables. Fisher's exact test was used when the expected cell size was < 5 .

To test the first and second hypotheses, we calculated mean levels and instabilities of sleep and affect variables across all study days ($M = 54$ days, ± 8 days). Instability of each variable was calculated by the mean squared successive differences (MSSD; Jahng, Wood, & Trull, 2008). The MSSD was chosen as the index of instability based on recommendations for its use in ecological momentary assessment studies of affect (for review see Ebner-Priemer, Eid, Kleindienst, Stabenow, & Trull, 2009). The nonparametric Mann–Whitney *U* test was used for between-groups comparisons; nonparametric analyses were used because the majority of sleep and affect time series were highly skewed and non-normal even after attempts at normalizing transformations. A Bonferroni multiple-testing correction was applied to each set of comparisons individually, that is, a significance level of $.05/8 = .00625$ was applied to each group of comparisons on sleep, and a significance level of $.05/2 = .025$ was applied to each group of comparisons on affect.

To test the third hypothesis, we conducted a mutual information (MI) analysis. MI is a statistical measure of dependency between two random variables (Gray, 1990). An advantage of MI over typical correlation analyses is that MI includes linear as well as nonlinear relationships between two variables, and hence may be more appropriate in situations where joint normality of two random variables is not a plausible assumption, as is the case in the present study. A nonparametric measure of MI (Peng, Long, & Ding, 2005) was computed for each pair of sleep and affect variables for each subject. Differences in between-groups levels of MI were tested using the Mann–Whitney *U* test, with a Bonferroni correction applied to each set of comparisons separately. For interpretability, MI scores were normalized to fall between zero and one; zero indicates independence and one indicates a deterministic relationship between two variables (Zhou, Thompson, & Siegle, 2009). MI analyses were performed in MATLAB Version 7.10.0 (using code available from Peng et al., 2005). All other analyses were completed using SPSS Version 18.0 or R Version 2.13.

Results

Demographic and Baseline Data

Demographic characteristics and baseline clinical and sleep data of participants are presented in Table 1. The bipolar and control groups did not differ significantly in age, gender, annual household income, or employment status. Despite efforts to equate the two groups on all demographic variables, the groups differed with respect to marital status (a greater proportion of controls were married or cohabiting with a partner). There was a trend for a group difference on ethnicity; a near significant ($p = .064$) greater proportion of control participants were ethnic minorities. Bipolar participants exhibited significantly more depressive and manic symptoms than control participants. All symptom scores were well below established clinical cutoffs (Rush et al., 1996; Young et al., 1978). Bipolar participants obtained significantly higher scores than controls on the ISI (Bastien et al., 2001) and PSQI (Buysse et al., 1989) indicating that interepisode bipolar participants experienced more sleep difficulties than controls upon study entry. The percentage of bipolar participants scoring at levels indicative of clinically significant sleep difficulties (i.e., above 7 on the Insomnia Severity scale and above 5 on the Pittsburgh Sleep Quality Index)

was 37.5% (12/32) and 53.1% (17/32), respectively. The average Somatotherapy Index score in the bipolar group was fairly low.

Daily Measures of Sleep and Affect

Table 2 presents means and variability of each sleep and affect variable for bipolar and control groups, as well as the unadjusted *U* test values of the between group comparisons. Asterisks indicate comparisons that survived Bonferroni's correction ($p < .00625$ for sleep variables, $p < .025$ for affect variables). As measured by actigraphy, bipolar participants exhibited significantly more variable time in bed than controls. As measured by sleep diary, bipolar participants reported significantly longer and more variable total wake time and more variable sleep efficiency than controls. Bipolar participants also reported significantly higher and more variable levels of negative affect than controls. There were no significant group differences in mean level or variability of positive affect.

As shown in Table 3, both actigraphy and diary sleep variables shared significantly more information with negative affect in bipolar participants compared to controls. Specifically, actigraphy measured longer sleep onset latency and longer wake after sleep onset were coupled with higher negative affect more strongly in the bipolar group than in the control group. For subjectively measured variables, longer wake after sleep onset, greater number of awakenings, and lower sleep efficiency were coupled with higher levels of negative affect more strongly in the bipolar group than in the control group. After adjustment for the potential confounds of marital status and ethnicity the coupling of actigraphy-measured sleep onset latency with negative affect and the coupling of diary-measured wake after sleep onset and sleep efficiency with negative affect remained highly significantly different between the two groups (p s ranging from .025 to .009).

We employed nonparametric MI analyses due the highly non-normal and nonlinear nature of the data and due to the heterogeneity of responses across subjects. However, to further investigate sleep-affect coupling of variables exhibiting significant differences between groups in the MI analyses, we performed post hoc analyses using linear mixed effects models with log-transformed negative affect as the dependent variable and sleep measures as time-varying random effects. Diagnosis was entered as an independent variable and interacted with the respective sleep measure. Results from these post hoc analyses confirmed the significant interactions of diagnosis with diary-measured wake after sleep onset (coef = 0.29, $p < .0001$), number of awakenings (coef = 0.26, $p = .0001$), and sleep efficiency (coef = -0.20, $p = .007$). Actigraphy-measured sleep onset latency (coef = 0.08, $p = .226$) and wake after sleep onset (coef = 0.11, $p = .085$) were in the same direction as with the MI analyses but not significant.

In order to better understand the potential role of psychotropic medications in the bipolar group we conducted Spearman correlations to examine whether Somatotherapy Index scores related to illness severity indices, or to any of the dependent variables found to significantly differ between the bipolar and control groups. Medication levels were correlated with mean levels of negative affect ($r = .43$, $p = .014$, $n = 32$), and the coupling of diary-measured wake after sleep onset with negative affect ($r = .53$, $p = .002$, $n = 32$). Medication levels were also correlated with mania symptom severity at the second and third (final) lab visits (r s = .37 and .41, respectively, p s < .05, $n = 32$). Medication levels were not significantly correlated with symptom severity at baseline, nor with depression symptom severity at the subsequent lab visits. Medication levels were not correlated with age of illness onset, number of manic or depressive episodes, or number of psychiatric hospitalizations.

Discussion

Disturbed sleep and affect are common and prognostic features of bipolar disorder, yet few longitudinal studies have examined these disturbances conjointly, using prospective daily sampling. The current study collected daily affect ratings and both subjective and objective estimates of sleep over an eight week period in order to clarify which components of sleep and affect are disturbed in interepisode bipolar disorder, and to prospectively characterize the relationship between sleep and affect using time dependent analysis.

Consistent with our first and second hypotheses, interepisode bipolar participants exhibited greater disturbances in sleep and affect. With regard to sleep, bipolar participants exhibited more variable time in bed as measured by actigraphy, and reported longer and more variable periods of wakefulness during the night, and more variable sleep efficiency than controls. These findings are in line with previous research indicating that even outside of acute episodes of illness bipolar disorder is characterized by pervasive sleep difficulties (Harvey et al., 2005; Millar et al., 2004), including sleep variability (Eidelman, Talbot, Gruber, Harvey, 2010; Jones et al., 2005; Meyer & Maier, 2006). The current study specifies the precise subjective and objective sleep parameters that are disturbed during this period. As has been documented by previous research (Harvey et al., 2005), both subjectively and objectively estimated parameters are crucial counterparts for the assessment of sleep. Consistent with this view, we found group differences in reports of sleep that were not paralleled in actigraphic measurement. The discrepancy between subjective and actigraphic measures of sleep has been found before (e.g., Harvey et al., 2005; Millar et al., 2004) and may reflect misperception of sleep among bipolar patients and/or that actigraphy is not sufficiently sensitive to capture the sleep disturbance in bipolar disorder (Harvey & Tang, 2012).

With regard to affective disturbance, bipolar participants reported higher and more variable negative, but not positive, affect compared to healthy controls. Elevated levels of negative affect and greater affective lability have been previously reported in subsyndromal bipolar samples (e.g., Lovejoy & Steuerwald, 1995). People with bipolar disorder may be more affectively reactive to environmental stressors than are nonpsychiatric populations (Depue, Kleinman, Davis, Hutchinson & Krauss, 1985; Myin-Germeys et al., 2003). For instance, interepisode bipolar patients show greater changes in positive and negative affect in response to experiences of success or failure when compared with controls (Pavlova, Uher, Dennington, Wright, & Donaldson, 2011). Our findings are specific to negative affect, suggesting that disturbances in negative affect may be particularly common in bipolar disorder. This is consistent with recent findings gathered via experience sampling that document increased negative affect in interepisode bipolar individual as compared to controls (Havermans et al., 2010; Talbot et al., in press). Further research is needed to elucidate potential reasons for disturbance in negative affect during the interepisode period.

Our findings point to the importance of the relationship between sleep and affect in the interepisode phase of bipolar disorder. Consistent with our third hypothesis, and with previous theoretical viewpoints (Harvey, 2008; Wehr, 1990), we found greater coupling of sleep and affect in interepisode bipolar participants relative to controls. Specifically, we found this for the coupling of sleep onset latency, wake after sleep onset, and sleep efficiency with negative affect. These effects were retained after controlling for potential confounds. Our findings that disturbances in sleep are closely tied to higher levels of negative affect are congruent with findings in healthy samples. Specifically, during a weeklong study in which sleep was restricted in healthy participants, mood progressively declined as sleep loss accumulated (Dinges et al., 1997). Similarly, sleep loss intensified negative affective response to daytime stressors among medical residents (Zohar et al., 2005). Given that sleep loss contributes to increased negative affect in healthy samples, it

seems likely that individuals with a vulnerable emotional-regulation system would experience comparable, if not larger, effects on negative affect.

The findings of the present study lend further support to the idea that affect and sleep disturbance in bipolar disorder are closely interlinked, with sleep disturbance contributing to increased negative affect and negative affect contributing to increased sleep disturbance. This is noteworthy given that the adverse impact of negative affect associated with worry on sleep has been well documented (e.g., Gross & Borkovec, 1982; Tang & Harvey, 2004). Past experimental research has also shown that a sad affect induced prior to sleep was not associated with greater sleep disturbance in an interepisode bipolar sample (Talbot et al., 2009). Perhaps sleep in interepisode bipolar disorder becomes particularly disturbed in the presence negative affect associated with a high level of arousal (such as anxiety or irritability) or under naturalistic conditions (Talbot et al. involved an experimental induction of mood).

Several limitations should be acknowledged. First, the sample size was relatively small and may have limited statistical power. Our focus on the interepisode period of bipolar disorder by definition restricted participant eligibility to individuals maintaining low levels of symptoms throughout the course of the prospective assessment period and thus, precluded examination of the effects of sleep or sleep-affect coupling on episode onset. Prior research has prospectively linked shorter and more variable sleep duration to more severe mania and depression symptoms (e.g., Gruber et al., 2011; Perlman et al., 2006). Replication with a larger sample and with follow-ups to examine effects on episode relapse is warranted.

Second, although we were able to match groups on most demographic variables, the groups differed significantly in marital status, and near significantly in ethnic composition. However, most findings remained after controlling for these variables in addition to a conservative Bonferroni's correction. Nevertheless, it will be important for the study results to be replicated in larger samples matched on marital status and ethnicity.

Third, our assessment of medication use was based on self-report. As medication compliance is a known problem in bipolar samples (e.g., Colom et al., 2000; Keck, McElroy, Strakowski, Bourne, & West, 1997), the reliability of this information would be improved with the use of blood serum level testing, or by validation with medical records. Indeed, the average Somatotherapy Index score in the bipolar group was fairly low, in part because blood serum levels for mood stabilizers were not available.

Fourth, medication use may have a confounding effect on both sleep and affect. All but two bipolar participants were being treated with medication and controls were not. It would be neither ethical nor representative to conduct research on a medication-free bipolar group. As noted, bipolar participants were treated with a heterogeneous group of medications. Subgroup analyses would be required to examine effects of individual medications on sleep or affect. The relatively small sample limits the statistical power available for such analysis. In addition, many medications can have sedating or alerting effects (e.g., Physicians' Desk Reference Staff, 2007) making it difficult to create sedating-medication and alerting-medication subgroups. Furthermore, the majority of our bipolar participants (nearly 60%) were taking more than one medication, potentially creating unknown interaction effects. Nevertheless, we examined the role that medication levels played in our data. We found that higher levels of medication were related to more negative affect and greater coupling of diary-measured wake after sleep onset with negative affect. Medication levels were also related to more severe mania symptoms during the daily assessment period. It may be the case that those who require a more intensive medication regimen to remain interepisode also experience more affective disturbance and more sleep-affect coupling. Given the relatively

small sample, however, these findings can only be considered as suggestive. Although the potential confounding effect of medication remains, one of the recommended strategies to address this confound is a within-subject design, as was our design, such that intersubject variability in medication use is minimized (Harvey, Talbot, & Gershon, 2008).

Despite these limitations, the current study is the first to investigate the relationship between naturally occurring sleep and affect in a sample of interepisode bipolar adults using daily measures of the entire set of “gold standard” sleep parameters (Buysse et al., 2006) and positive and negative affect collected over the course of eight weeks. Our results indicate that the coupling of sleep onset latency, wake after sleep onset, and sleep efficiency with negative affect may be important features of the interepisode period of bipolar disorder. Given that sleep disturbance and dysregulated negative affect are known to have adverse effects on the course of bipolar disorder, the coupling of these specific sleep parameters with negative affect may contribute to sustained impairment during interepisode periods. If this is the case, monitoring the relationship between interepisode sleep and negative affect for patterns of increased coupling may identify important targets for interventions.

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Table 1

Demographic Characteristics and Baseline Clinical and Sleep Data for Bipolar and Control Participants

	Group		Statistical Test
	Bipolar (<i>n</i> = 32)	Control (<i>n</i> = 36)	
Mean age in years (<i>SD</i>)	34.7 (10.5)	33.3 (12.6)	$U = 691.5, p = .479$
Gender			$\chi^2(1) = .66, p = .468$
Male	12	17	
Female	20	19	
Ethnicity (<i>N</i>)			$\chi^2(5) = 10.44, p = .064$
African American	3	1	
Asian	3	12	
Hispanic	3	6	
Native American	1	0	
Caucasian	20	17	
Biracial/Other	2	0	
Marital Status (<i>N</i>)			$\chi^2(2) = 14.30, p = .001$
Single	22	19	
Married/live-in partner	1	14	
Divorced/separated/widowed	9	3	
Annual Household Income ^a (<i>N</i>)			$\chi^2(4) = 3.71, p = .447$
Less than \$25,000	8	12	
\$25,000–50,000	14	12	
\$50,000–75,000	2	5	
\$75,000–100,000	5	2	
Over \$100,000	3	2	
Employment Status (<i>N</i>)			$\chi^2(3) = 1.40, p = .705$
Full-time	10	15	
Part-time	10	8	
Unemployed/retired	7	6	
Student	5	7	
Mean Symptom Values (<i>SD</i>)			
Depressive symptoms (IDS-C) ^b	8.6 (4.7)	2.2 (1.9)	$U = 1002.5, p < .001$
Manic symptoms (YMRS) ^b	3.2 (3.0)	.7 (1.3)	$U = 833.5, p < .001$
Insomnia Severity Index score	6.8 (4.7)	1.9 (2.3)	$U = 945.5, p < .001$
Pittsburgh Sleep Quality Index Global score ^c	5.6 (2.9)	2.3 (1.3)	$U = 993.0, p < .001$
Mean Somatotherapy Index Score (<i>SD</i>)	1.8 (1.4)	—	

^aThree control group cases missing annual household income.^bOne control group case missing depressive and manic symptom scores.^cOne bipolar group case missing Pittsburgh Sleep Quality Index scores. U = Mann-Whitney U Test; IDS-C = Inventory of Depressive Symptomatology-Clinician Rating; YMRS = Young Mania Rating Scale.

Table 2

Means and Instability of Sleep and Affect Variables for Bipolar and Control Participants

	Group		Mann-Whitney <i>U</i> Test Statistic
	Bipolar (<i>n</i> = 32)	Control (<i>n</i> = 36)	
Means of actigraphic sleep variables (<i>SD</i>)			
Sleep onset latency (minutes)	12.0 (11.6)	7.3 (3.5)	735, <i>p</i> = .051
Wake after sleep onset (minutes)	96.9 (53.5)	85.6 (27.9)	616, <i>p</i> = .623
Terminal wakefulness (minutes)	15.6 (8.0)	14.9 (7.0)	603, <i>p</i> = .740
Total wake time (minutes)	124.4 (56.7)	107.2 (27.6)	666, <i>p</i> = .269
Time in bed (minutes)	503.9 (70.6)	468.0 (50.7)	756, <i>p</i> = .027
Total sleep time (minutes)	379.5 (62.1)	360.8 (57.5)	677, <i>p</i> = .215
Number of awakenings	27.4 (7.5)	28.5 (5.6)	495, <i>p</i> = .320
Sleep efficiency	76.1% (9.4%)	77.2% (6.4%)	522, <i>p</i> = .507
Instability of actigraphic sleep variables in MSSD (<i>SE</i>)			
Sleep onset latency	562.9 (163.4)	215.1 (35.1)	704, <i>p</i> = .116
Wake after sleep onset	7187.5 (711.3)	5775.6 (696.6)	725, <i>p</i> = .067
Terminal wakefulness	745.6 (150.3)	478.7 (65.0)	641, <i>p</i> = .424
Total wake time	6723.4 (573.6)	5489.0 (652.2)	741, <i>p</i> = .043
Time in bed	21077.8 (2412.6)	14653.6 (2130.8)	804, <i>p</i> = .005*
Total sleep time	13805.0 (1586.7)	9973.9 (1034.2)	756, <i>p</i> = .027
Number of awakenings	149.9 (17.3)	126.7 (11.4)	643, <i>p</i> = .410
Sleep efficiency	154.0 (11.5)	157.2 (13.6)	580, <i>p</i> = .961
Means of subjective sleep variables (<i>SD</i>)			
Sleep onset latency (minutes)	17.5 (12.4)	10.7 (6.4)	761.5, <i>p</i> = .023
Wake after sleep onset (minutes)	17.4 (15.7)	9.0 (8.2)	787, <i>p</i> = .010
Terminal wakefulness (minutes)	27.0 (20.9)	20.0 (18.8)	733, <i>p</i> = .054
Total wake time (minutes)	61.9 (36.8)	39.8 (24.7)	826, <i>p</i> = .002*
Time in bed (minutes)	512.0 (66.9)	476.8 (45.5)	759, <i>p</i> = .025
Total sleep time (minutes)	451.5 (61.0)	437.9 (43.9)	673, <i>p</i> = .233
Number of awakenings	1.4 (0.8)	1.1 (0.9)	716, <i>p</i> = .085
Sleep efficiency	88.0% (6.3%)	91.3% (4.7%)	388, <i>p</i> = .021
Instability of subjective sleep variables in MSSD (<i>SE</i>)			
Sleep onset latency	631.4 (191.6)	233.2 (66.3)	764, <i>p</i> = .021
Wake after sleep onset	1347.6 (297.3)	449.8 (99.7)	734, <i>p</i> = .052
Terminal wakefulness	2105.6 (535.9)	1233.9 (334.4)	776, <i>p</i> = .014
Total wake time	4921.9 (914.0)	1892.9 (342.4)	855, <i>p</i> = .001*
Time in bed	19848.4 (2895.0)	15620.1 (3865.3)	774, <i>p</i> = .015
Total sleep time	18250.3 (2310.5)	13932.4 (3217.5)	789, <i>p</i> = .009
Number of awakenings	1.7 (0.2)	1.6 (0.2)	580.5, <i>p</i> = .956
Sleep efficiency	162.5 (25.8)	80.7 (13.7)	839, <i>p</i> = .001*
Means of affect variables (<i>SD</i>)			
Positive affect	24.4 (8.0)	27.3 (8.5)	467, <i>p</i> = .180

	Group		Mann-Whitney <i>U</i> Test Statistic
	Bipolar (<i>n</i> = 32)	Control (<i>n</i> = 36)	
Negative affect	22.5 (5.4)	17.5 (2.2)	955, <i>p</i> = .001 [*]
Instability of affect variables in MSSD (<i>SE</i>)			
Positive affect	55.1 (7.9)	37.4 (4.7)	713, <i>p</i> = .092
Negative affect	59.9 (20.1)	19.2 (3.2)	848, <i>p</i> = .001 [*]

Note. MSSD = Mean Square Successive Difference; *SD* = Standard Deviation; *SE* = Standard Error.

^{*}
 $p < .00625$ for sleep variables, $p < .025$ for affect variables. (Bonferroni correction)

Table 3

Means of Normalized Mutual Information (MI) Between Sleep and Affect for Bipolar and Control Participants

	Group		
	Bipolar (<i>n</i> = 32)	Control (<i>n</i> = 36)	Wilcoxon Rank Sum Test Statistic
Actigraphic sleep variables with positive affect			
Sleep onset latency	.26 (.10)	.22 (.09)	458, <i>p</i> = .150
Wake after sleep onset	.27 (.10)	.24 (.09)	488.5, <i>p</i> = .285
Terminal wakefulness	.24 (.09)	.23 (.08)	598, <i>p</i> = .793
Total wake time	.26 (.09)	.24 (.09)	528, <i>p</i> = .562
Time in bed	.29 (.10)	.24 (.07)	388, <i>p</i> = .021
Total sleep time	.28 (.08)	.24 (.08)	460, <i>p</i> = .157
Number of awakenings	.28 (.10)	.24 (.08)	474, <i>p</i> = .214
Sleep efficiency	.24 (.09)	.23 (.07)	579, <i>p</i> = .976
Actigraphic sleep variables with negative affect			
Sleep onset latency	.25 (.08)	.19 (.07)	330, <i>p</i> = .002 *
Wake after sleep onset	.24 (.08)	.21 (.09)	337, <i>p</i> = .003 *
Terminal wakefulness	.25 (.09)	.22 (.09)	493, <i>p</i> = .313
Total wake time	.25 (.10)	.22 (.06)	439, <i>p</i> = .094
Time in bed	.29 (.10)	.23 (.08)	399, <i>p</i> = .029
Total sleep time	.30 (.12)	.23 (.08)	374, <i>p</i> = .013
Number of awakenings	.26 (.09)	.23 (.08)	450, <i>p</i> = .124
Sleep efficiency	.25 (.10)	.20 (.07)	414, <i>p</i> = .047
Subjective sleep variables with positive affect			
Sleep onset latency	.24 (.11)	.24 (.11)	604, <i>p</i> = .737
Wake after sleep onset	.25 (.08)	.21 (.10)	423, <i>p</i> = .061
Terminal wakefulness	.24 (.10)	.24 (.11)	579, <i>p</i> = .976
Total wake time	.27 (.09)	.22 (.08)	404, <i>p</i> = .035
Time in bed	.26 (.07)	.27 (.08)	680, <i>p</i> = .205
Total sleep time	.28 (.09)	.27 (.10)	569, <i>p</i> = .937
Number of awakenings	.26 (.11)	.22 (.10)	446, <i>p</i> = .112
Sleep efficiency	.29 (.09)	.24 (.09)	368, <i>p</i> = .011
Subjective sleep variables with negative affect			
Sleep onset latency	.23 (.09)	.22 (.12)	509, <i>p</i> = .416
Wake after sleep onset	.26 (.12)	.18 (.09)	355, <i>p</i> = .006 *
Terminal wakefulness	.25 (.08)	.23 (.10)	572, <i>p</i> = .966
Total wake time	.29 (.08)	.23 (.09)	445, <i>p</i> = .109
Time in bed	.30 (.08)	.24 (.10)	474, <i>p</i> = .214
Total sleep time	.28 (.10)	.24 (.08)	473, <i>p</i> = .209
Number of awakenings	.26 (.12)	.20 (.12)	336, <i>p</i> = .003 *
Sleep efficiency	.29 (.09)	.22 (.09)	320, <i>p</i> = .001 *

Note. Mean values are presented. Standard deviations are in parentheses.

*
 $p < .00625$. (Bonferroni correction)