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McGlinchey, Eleanor Louise

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Circadian Rhythms and Clock Genes in Inter-episode Bipolar Disorder

By

Eleanor Louise McGlinchey

A dissertation submitted in partial satisfaction of the  
requirements for the degree of

Doctor of Philosophy

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Committee in charge:

Professor Allison G. Harvey, Chair

Professor Lance Kriegsfeld

Professor Ronald Dahl

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## Abstract

## Circadian Rhythms and Clock Genes in Inter-episode Bipolar Disorder

by

Eleanor Louise McGlinchey

Doctor of Philosophy in Psychology

University of California, Berkeley

Professor Allison Harvey, Chair

**Objectives:** Circadian rhythms are hypothesized to be disturbed in bipolar disorder (BD). However, the empirical evidence for this hypothesis is mixed. Hence, the goals of the current investigation were to extend and contribute to clarifying the literature on circadian rhythms in inter-episode BD by comparing proxies for circadian rhythm functioning in BD I and II individuals, relative to healthy controls.

**Methods:** Thirty-five adults diagnosed with inter-episode BD I and II were compared to 37 healthy controls of similar age and gender. All participants completed a questionnaire assessing chronotype, reported daily sleep and wake times for four weeks, and wore wrist actigraphy for four weeks in order to assess objective estimates of sleep and wake timing and to calculate the cosinor variables, MESOR, amplitude and acrophase, as proxies for circadian modulation of activity. Participants also provided a saliva sample in order to analyze DNA for polymorphisms of the clock genes PER3 and CLOCK.

**Results:** There were no significant differences between the BD and control groups on questionnaire reported chronotype, although there was a trend for significance such that BD individuals were more likely to report an evening chronotype. BD individuals exhibited more instability in sleep and wake timing as assessed by both sleep diary and actigraphy. There were no significant differences between the BD and control groups on any of the cosinor analysis variables; namely, MESOR, amplitude and acrophase. There was a trend for differences in MESOR among BD individuals who were carriers of the C-allele of the CLOCK gene. There were no differences in circadian cosinor variables for any of the genotype groups of PER3.

**Conclusions:** The current findings are not consistent with previous hypotheses that abnormal circadian activity rhythms are enduring (trait) characteristics of BD individuals. However, instability in sleep timing may be characteristic of the inter-episode period.

## Introduction

Bipolar disorder (BD) is a recurrent disorder that is characterized by episodes of depression and mania, interspersed with inter-episode periods (Goodwin & Jamison, 1990). BD is often life-threatening with approximately 1 in 5 individuals completing suicide (Isometsä, 1993). The lifetime prevalence of the BD spectrum is 3.9% (Kessler et al., 2005). After the onset of the disorder, individuals with BD who have been hospitalized spend approximately 20% of their life in episodes (Angst & Sellaro, 2000) and approximately 50% of their time unwell (Joffe, MacQueen, Marriott & Young, 2004). Not surprisingly, BD is ranked as one of the top 10 leading causes of disability worldwide (World Health Organization, 2001). Although there have been important advances in pharmacologic (Keck, 2000) and nonpharmacologic (Miklowitz & Johnson, 2006) treatments for BD, a high proportion of patients remain seriously symptomatic during the inter-episode period (MacQueen, Marriott, Begin, Robb, Joffe & Young, 2003) and the risk of relapse over five years is as high as 73% (Gitlin, Swendsen, Heller & Hammen, 1995). Hence, there is a need to uncover the mechanisms contributing to symptoms in the inter-episode period and to relapse into mania or depression. The current study delineates one possible mechanism by which BD is maintained; namely, circadian rhythm dysfunction.

It has long been hypothesized that dysfunction of circadian rhythms is associated with BD (Goodwin & Jamison, 1990). The proposal has been that a core circadian dysfunction results in disturbed sleep, which in turn precipitates illness episodes (Ehlers et al., 1993). It is important to note that a distinction between the sleep and circadian systems is inherent to this proposal (Harvey, 2008). According to Borbely's (1980) two process model, the sleep-wake cycle is regulated by two separate processes. The first process is the circadian process, also known as Process C, which regulates biological rhythms to approximately 24 hours. The second process is sleep's homeostat or Process S. Process S is accumulated during wakefulness, dissipates during sleep and regulates the duration and structure of sleep on the basis of the previous duration of sleep and wakefulness. The two-processes are interrelated and overlapping but are independent (Borbeley, 1982). Accordingly, the circadian and sleep systems need to be studied separately.

There are already multiple lines of evidence lending support to the role of sleep (Process S) in BD (see Harvey, 2008 and Plante & Winkelman, 2008 for review). For example, in a systematic review of prodromal symptoms in BD, Jackson et al. (2003) reported that BD patients identified sleep disturbance as the most common prodrome of mania and the sixth most common prodrome of depression. Longitudinal studies indicate day-by-day associations between sleep and mood in BD (Talbot et al., 2012; Gershon et al., in press). Additionally, experimental and case studies have reported that induced sleep deprivation is associated with the onset of hypomania or mania in a high proportion of patients (Wehr, Goodwin, Wirz-Justice, Breitmaier & Craig, 1982; Wehr, Sack & Rosenthal, 1987). Moreover, sleep remains disturbed even during the inter-episode phases of BD (Millar, Espie & Scott, 2004; Harvey et al., 2005). There are many potential contributors to disturbed sleep in BD. One potential contributor may be timing of sleep within the 24 hour day, given that sleeping at an adverse circadian phase has consequences on both physical and emotional health in otherwise healthy individuals (Ohayon, Lemoine, Amaud-Briant & Dreyfus, 2002). In particular, the most adverse health consequences are associated with instability in sleep timing, when an individual changes the time they go to bed and wake up from day to day (Drake, Roehrs, Richardson, Walsh, & Roth, 2004). Sleep timing has not been examined in BD, but is hypothesized to be particularly unstable and inconsistent

given that the timing of sleep can be altered by both biological factors (i.e., the circadian system) and behavioral factors (Wittmann, Dinich, Merrow, & Roenneberg, 2006).

Empirical evaluation of the circadian system's role in BD has been wrought with challenges. One challenge has been that the gold standard methods for measuring the circadian system, such as forced desynchronization (Dijk & Cajochen, 1997) and constant routine protocols (Monk, Buysse, Frank, Kupfer, Dettling & Ritenour, 1994) are not used in BD populations. These protocols are inherently emotionally and physically challenging, raising ethical and clinical concerns for participants with a severe mental illness (Harvey, Murray, Chandler, & Soehner, 2010). Consequently, methods that have been used to study the circadian system in BD include self report questionnaires, as well as fitting repeated measures of melatonin, cortisol, temperature and activity via actigraphy to the widely used cosinor modeling analysis. The latter entails fitting an oscillating curve to a temporal variable using 24-hour periodicity. It supplies the midline estimating statistic of rhythm (MESOR; 24-hour adjusted mean value or y-intercept), the amplitude (half the peak-to-trough difference), and acrophase (time of day for peak activity), for each individual sampled.

A finding that has emerged from research using self-report questionnaires has been an association between BD and a preference for a delayed circadian phase (e.g., Mansour et al., 2005). However, questionnaires can only be regarded as approximations because they are influenced by factors other than the endogenous circadian rhythm, including the person's memory, the time of day and recent experience (Schacter, 1999). In one study using melatonin as a marker for circadian rhythms, inter-episode BD patients exhibited lower average melatonin levels and a later peak time for melatonin during the night relative to a healthy comparison group (Nurnberger, Adkins, Lahiri, Mayeda, Hu et al, 2000). However, the measurement period occurred only on one night and the effect of bright light versus dim light was being tested simultaneously, rendering the results difficult to interpret. In another study indexing cortisol every hour for 24 hours, patients experiencing current symptoms of mania or depression exhibited higher mean circadian cortisol levels relative to a healthy control group, but there were no differences between the inter-episode bipolar and control groups (Cervantes, Gelber, Kin, Nair, & Schwartz, 2001). Research on body temperature measurements have yielded similarly inconsistent results with one study suggesting a phase advance in BD (Avery et al., 1982), others a phase delay (e.g., Daimon et al., 1992) and in one study, no phase difference (Monk et al., 1994) when compared to a healthy control group. More recently, actigraphy has been used to determine circadian rhythms in BD (Salvatore et al., 2008; Jones et al., 2005). Relative to a healthy control group, Salvatore et al. (2008) and Jones et al. (2005) found overall lower mean circadian activity in individuals with inter-episode BD. However, the two studies report conflicting results with regard to differences in circadian amplitude and acrophase. Moreover, the measurement period in both studies was relatively short, less than 7 days in both studies. Additionally, the methods of analysis for circadian modulation of activity differed in both studies.

The lack of consensus from the studies reviewed above is most likely due to differences in (1) measurement methods of circadian rhythm, (2) sampling periods and frequencies, (3) working definitions of what is considered endogenous circadian rhythm function versus behaviors that may be only partially regulated by the circadian system, and (4) methods of analysis. In view of these differences in methodology, one aim of the current study was to expand the knowledge base regarding circadian rhythms and related behaviors in BD by utilizing self-report questionnaires, daily diary reports of sleep timing and daily hour-by-hour activity

levels via actigraphy over a *one-month* period. Moreover, linear mixed-effects cosinor analysis (Mikulich et al., 2003) was employed so that the circadian variables could be estimated while accounting for systematic inter-individual differences.

A burgeoning area of research is the interaction between Clock genes and circadian rhythms. Associations reported include relationships between the Clock genes PER3 and CLOCK with sleep phase disorders (Ebisawa et al., 2001) and preferred sleep timing (Katzenberg et al., 1998; Archer et al., 2003). Specifically, in healthy individuals, the variable number tandem repeat (VNTR) polymorphism in PER3, where a 54-nucleotide coding region motif is repeated in 4 or 5 units, has been linked with multiple phenotypic parameters. Each individual has a 4r/4r, 4r/5r or 5r/5r genotype on PER3. The shorter, 4-repeat allele (the 4r/4r genotype) is associated with evening preference relative to individuals with a 4r/5r or 5r/5r genotype (Archer et al., 2003). Furthermore, evidence suggests that PER3 (Nievergelt et al., 2006) and CLOCK (Roybal et al., 2007; Benedetti et al., 2007) are associated with BD. Benedetti et al. (2007) found that among depressed BD inpatients, carriers of the C-allele of CLOCK 3111 T/C SNP (rs1801260) experienced later sleep and activity patterns relative to those individuals who were TT homozygotes. Each individual has a CC, CT or TT genotype on CLOCK. However, sleep and activity patterns have not been systematically examined through cosinor analysis or investigated for longer than 1 day among genotype groups in individuals with BD. Moreover, Benedetti et al. (2007) reported that once patients returned to inter-episode symptom levels, their sleep and activity patterns were similar to the BD patients who were not carriers of the C-allele. The current literature on the influence of clock genes on circadian rhythms in BD needs further clarification. On the one hand, prior research on individuals with BD and animal studies (reviewed above) suggest an association between BD and in-episode symptoms with both PER3 and CLOCK genes. On the other hand, only one study has investigated circadian rhythm activity among inter-episode BD individuals with regard to clock genes (Benedetti et al., 2007) and results suggest that there might not be differences in genotype groups once symptoms stabilize. Hence, the current study sought to further knowledge by clarifying the association between PER3 and CLOCK with indices of circadian rhythms (MESOR, amplitude and acrophase) using cosinor analysis in inter-episode BD.

## **The Current Study**

The goals of the current investigation were to extend and clarify the literature on circadian rhythms and related behaviors in BD. The study had four aims. The first aim was to use a psychometrically validated questionnaire to examine differences in chronotype between inter-episode BD participants and healthy controls. The hypothesis tested was that inter-episode BD participants would report a preference for a delayed circadian phase relative to healthy controls (e.g., Mansour et al., 2005). The second aim was to examine, over a one-month period using sleep diary and actigraphy, the instability of sleep timing behavior in inter-episode BD compared to healthy controls. The hypothesis tested was that the BD group would exhibit more instability, relative to the control group (e.g., Monk et al., 1994). The third aim was to examine, over a one-month period via actigraphy, the differences between circadian modulation of activity in inter-episode BD participants relative to healthy controls. The hypothesis tested was that BD participants would display lower mean circadian activity (referred to as MESOR), lower peak activity (referred to as amplitude) and phase-delayed rhythms of activity (referred to as acrophase), indicating circadian rhythm abnormalities in inter-episode BD (e.g., Jones et al,

2005). The final aim was to examine the influence of two clock genes (CLOCK and PER3) on the circadian modulation of activity over a one-month period in inter-episode BD relative to the control group. The hypothesis tested was that inter-episode BD participants who carry a C-allele of the CLOCK gene would display more circadian rhythm abnormalities indexed by actigraphy over a one-month period, relative to BD participants who are TT homozygotes and to the control group (Benedetti et al., 2007). Also, inter-episode BD participants with a 4r/4r genotype on PER3 were predicted to display more circadian rhythm abnormalities relative to BD participants with a 4r/5r or 5r/5r genotype and to the control group (Archer et al., 2003).

## Methods

### Participants

Participants included 35 adults (ages 18-65) with bipolar I or bipolar II disorder who were currently inter-episode and 37 healthy adults with no history of psychiatric or sleep disorders. Two other papers report findings from this study (Gershon et al., in press; Eidelman et al., in press). The unique contribution of the present paper is the focus on sleep timing and circadian rhythms, which is conceptually and practically different from the other papers.

Participants were recruited through internet advertisements and flyers distributed in the community. A telephone interview was completed to screen for eligibility. Potential participants were screened for, and excluded from, participation on the basis of: history of severe head injury, stroke, neurological disease, severe medical illness (e.g., autoimmune disorder), current mood episode (depression, mania), or current alcohol or substance abuse or dependence. Individuals who were considered likely to be eligible based on the initial telephone screen were invited to the laboratory for an extensive diagnostic interview session. Absence of psychiatric exclusionary criteria was confirmed at the first study visit based on the Structured Clinical Interview for DSM-IV-TR (SCID; First et al., 1995).

Individuals in the BD group were eligible to participate if they (a) met DSM-IV-TR criteria for a diagnosis of bipolar I or bipolar II disorder (American Psychiatric Association, 2000) based on the SCID; (b) did not meet criteria for a diagnosis of current substance or alcohol abuse or dependence in the past six months based on the SCID; and (c) did not meet criteria for narcolepsy, sleep apnea, restless leg syndrome or periodic limb movement disorder based on the Duke Structured Interview for Sleep Disorders (DSISD; Edinger, et al., 2004). In addition, BD participants were included only if they met criteria for inter-episode symptom cutoffs based on prior research (Chengappa, et al., 2003; Thompson, et al., 2005): a score of less than 12 on the Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978) and a score of less than 24 on the Inventory of Depressive Symptomatology, Clinician Rating (IDS-C; Rush, Gullion, Basco, Jarrett, & Trivedi, 1996). All BD participants were required to be in the care of a psychiatrist and information on medication was collected. Participants in the BD group were taking an average of 2.2 psychiatric medications each. Although anti-depressant, antipsychotic, and mood-stabilizing medications are likely to influence sleep and circadian rhythms, temporary discontinuation would have been impractical (given long washout/titration periods), unrepresentative (Philips, Travis, Fagiolini, & Kupfer, 2008) and unethical (given health-related risks of BD patients being unmedicated).

Participants in the control group were eligible if they (a) did not meet DSM-IV-TR criteria for any past or current Axis I disorder; (b) did not meet criteria for any past or current



sleep disorder based on the DSISD; and (c) had scores of less than 12 on the YMRS and less than 24 on the IDS-C.

## Measures

**Structured Clinical Interview for DSM-IV (SCID;** First, et al., 1995). The SCID is a semi-structured interview designed to assess DSM-IV diagnostic criteria for Axis I disorders. The SCID has shown good reliability for the majority of disorders it covers (Skre, Onstad, Torgersen, & Kringlen, 1991; Williams, et al., 1992). Trained doctoral students and a postdoctoral fellow in psychology administered the SCID to all participants to assess current and lifetime Axis I disorders. Seventeen randomly selected audiotapes of SCID interviews were rated by a set of independent reviewers in order to check diagnostic reliability. These were randomly selected equally for the BD and control participants. Ratings matched 100% ( $\kappa = 1.00$ ) of the primary diagnoses made by the original interviewer.

**Duke Structured Interview for Sleep Disorder (DSISD;** Edinger, et al., 2004). The DSISD is a semi-structured interview that assesses research diagnostic criteria for sleep disorders. The DSISD has been shown to have good reliability and validity (Edinger, et al., 2009). This interview was used to assess sleep disorders in all participants.

**Young Mania Rating Scale (YMRS;** Young, et al., 1978). The YMRS is an 11-item measure used to assess the severity of manic symptoms. It has been shown to have good reliability and validity (Young, et al., 1978). The YMRS was administered to assess inter-episode status of the BD participants. Scores range from 0-60. We used the cut-off score 12 for mild symptoms in order to ensure inter-episode status throughout the one-month study period (Young et al., 1978).

**Inventory of Depressive Symptomatology, Clinician Rating (IDS-C;** Rush, et al., 1996). The IDS-C is a widely-used 30-item instrument assessing depressive symptoms. The measure has demonstrated good reliability and validity (Rush, et al., 1996). It was administered to assess inter-episode status in the BD group. Scores can range from 0-90. We used the cut-off score 24 for mild symptoms in order to ensure inter-episode status throughout the one-month study period (Rush et al., 1996).

**Chronotype.** Morning- versus evening- chronotype was assessed using the Composite Scale (CS), a validated adaptation of the Horne-Östberg scale (Horne and Östberg, 1976; Smith et al., 1989). This self-report questionnaire gauges diurnal preference for activity and is composed of 13 items rated on a scale of 1 to 5. Scores range from 13 to 55, with higher scores indicating greater “morningness” and lower scores indicating “eveningness.” In a sample of 477 participants who were given both scales, the correlation between the original Horne-Östberg scale scores and CS scores was found to be 0.95 (Smith et al., 1989). In the present study, the CS score was regarded as a continuous variable measuring the degree of morningness/eveningness and as a categorical variable, whereby the scores of the top 25% of participants are considered morning types, the bottom 25% are evening types and the middle 50% are categorized as intermediate (Smith et al., 1989).

**Medication treatment.** The names and dosages of each participant’s medications were reported at baseline. Additionally, participants indicated the frequency and duration of medication use. The Somatotherapy Index (Bauer et al., 1997) was used to assess the adequacy of treatment on a 5-point scale (0-4), with higher scores indicating a more intense medication regimen. Scores take into account the type and dose of each medication, as well as the

combination of each medication with other medications. Specifically, the Somatotherapy Index score is obtained by: determining the type and dose of all medications participants report taking in the past month; coding each as an antidepressant, lithium, valproate, carbamazepine, or an alternative therapy (this category includes Gabapentin and Lamotrigine among other agents); and then calculating the Somatotherapy Index score by combining category levels (e.g., based on the coding system, if a lithium level is coded as a 1 and the alternative therapy level is coded as a 4, the Somatotherapy Index score is a 4). The level of each coded category is scored on a scale of 0 to 4, based on dose or number of therapies. In order to rate the level of lithium, valproate, or carbamazepine higher than a 1, blood serum levels of the medications are required. Antipsychotic levels are coded separately and are not considered when calculating the overall Somatotherapy Index score. The Somatotherapy Index is reliable and has been used in bipolar samples (e.g., Sajatovic, Bauer, Kilbourne, Vertrees, & Williford, 2006; Perlman, Johnson, & Mellman, 2006). In the present study, the antidepressant and alternative treatment subscales were coded on a scale ranging 0 to 4 (low to high dose/number of therapies), whereas the mood stabilizer subscales were rated dichotomously (treatment is absent or present) because blood serum levels for these medications were not available. In addition to the average Somatotherapy Index score obtained across the three study visits, subscales were coded to assess whether participants were receiving antidepressant, mood stabilizer, or alternative (e.g., lamotrigine) treatment.

**Sleep Diary.** The sleep diary followed standard recommendations for sleep research (Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006; Carney et al, 2012). The sleep diary included questions to assess ‘Sleep onset time’ and ‘Morning wake time.’ Sleep onset time was calculated by subtracting the indicated time it took to fall asleep from the reported bedtime. The midpoint between sleep onset and wake up (midsleep) was also calculated. Midsleep has been recognized as the phase reference point for sleep (see also Benoit et al., 1981). Midsleep has also been reported as the best phase anchor point for melatonin onset (Terman et al., 2001). The questions in the sleep diary have been shown to be reliable estimates (Morin & Espie, 2003; Carney et al, 2012) and are considered the gold standard subjective measure of sleep (Buysse, et al., 2006).

**Actigraphy.** To gather an objective estimate of sleep and circadian activity levels, participants wore an actigraphy watch (Mini Mitter AW64 Actiwatch Inc.). Actigraphs are wristwatch-like devices that provide an estimate of the sleep/wake cycle and activity levels by measuring movement (sampled in 60 second epochs). Data are stored in the watch’s embedded miniaturized accelerometer, downloaded, and used to estimate sleep parameters and activity levels using Respironics Actiware Version 5.5 (Copyright 2004-09, Respironics, Inc.). The correlation between actigraphy- and polysomnography-defined sleep estimates ranges from .88-.97 in adult normal sleepers (Cole, Kripke, Gruen, Mullaney, & Gillin, 1992; Jean-Louis et al., 1997), has been validated against polysomnography in bipolar individuals (Kaplan et al., in press), and has been successfully used to measure sleep in a range of clinical samples, including inter-episode bipolar patients (e.g., Gershon et al., in press; Harvey et al., 2005; Millar, Espie, & Scott, 2004). It provides the same sleep estimates that the sleep diary produces. Additionally, actigraphy provides indices of activity intensity and has been successfully used to measure activity levels in clinical samples, including bipolar patients (e.g., Jones, Hare, & Evershed, 2005). Minute-by-minute raw activity values were analyzed for each participant’s average activity level for each hour in the 24 hour day. The weight per unit of mass or g-force (G) is used

for these analyses. Actigraphy is ideal for naturalistic assessment of sleep and activity, as it is non-invasive and capable of storing large amounts of continuously collected data.

## Genotyping

**DNA Analysis of CLOCK.** The SNP markers were genotyped using TaqMan® SNP Genotyping Assays (Applied Biosystems, Foster City, CA, [www.appliedbiosystems.com](http://www.appliedbiosystems.com)) functionally tested by Applied Biosystems and available on demand. TaqMan® PCR reactions were conducted with 2.5uL Universal Master Mix Amperase® UNG, between 0.083uL and 0.125uL Taqman 40X or 20X probe mix and 1ul of DNA normalized to 10ng/ul, with water added to bring the volume up for a 5uL total volume. The PCR conditions for the TaqMan® SNP Genotype Assays were: one enzyme activation step at 95.0°C for ten minutes, and 40 alternating cycles of denaturation at 95.0°C for 15 seconds and reannealing and extension at 60.0°C for one minute. All PCR reactions and allelic discrimination reactions were performed on an ABI 7900HT Real-Time PCR System (Applied Biosystems, Foster City, CA) and analyzed using SDS 2.3 software (Applied Biosystems, Foster City, CA). The unrestricted PCR product (TT genotype) has a size of 221 bp; complete restriction (CC genotype) produces bands of 125 and 96 bp.

**DNA Analysis of PER3.** The primers to amplify the target region were reported previously (Ebisawa, et al. 2001) and were tagged with a M13 primer universally tagged for a generic FAM fluorescence. The samples were amplified with the primers in a 2ul reaction using Platinum Taq DNA Polymerase (Invitrogen) with 10ng of DNA on the 9700 thermal cycler (Applied Biosystems, Foster City, CA) with a PCR method of an enzyme activation step of 95° for 5 minutes, followed by 14 alternating cycles of denaturation, reannealing and extension at 94° for 20 seconds, 65° for 20 seconds and 72° for 45 seconds. This was followed by a second set of 35 alternating cycles of denaturation, reannealing and extension of 94° for 20 seconds, 58° for 20 seconds and 72° for 45 seconds, with an additional extension hold at 72° for 10 minutes. The PCR products were then diluted to 1:12, and the diluted product was denatured in a PCR method of 95° held for 5 minutes in a mixture of 1ul diluted product and 5ul 1000ROX size standard (Bioventures) and formamide (mixed in a ratio of 0.35ul:12ul) the resulting denatured product was run on the 3730xl DNA Analyzer (Applied Biosystems, Foster City, CA). The fragment data were viewed and analyzed with the GeneMapper program (Applied Biosystems, Foster City, CA).

## Design and Procedure

All procedures were approved by the University of California, Berkeley, Committee for the Protection of Human Subjects. After completing the initial telephone screen, participants who appeared likely to be eligible were invited to the laboratory for a baseline visit. During this visit participants signed informed consent and were interviewed by postdoctoral or doctoral student interviewers to assess the diagnostic status and symptom severity using the SCID, the DSISD, the YMRS, and the IDS-C. Once eligibility was determined by these measures, participants completed the demographics, medication, and CS questionnaire. Eligible participants then provided a saliva sample via Oragene collection kit (DNA genotek, Ontario, Canada). Upon completion of the baseline visit, eligible participants were sent home to complete the sleep diary each morning and wear the actiwatch continuously for one month. Participants were required to

call the lab each time they completed the morning sleep diary in order to time stamp their responses daily. At the end of the month, participants returned to the lab. The YMRS and IDS-C were re-administered to ensure continued inter-episode status, and data on medication use was collected. Participants who were found to be more than mildly hypomanic (defined as a YMRS score more than 12; e.g., Suppes et al., 2005) or mildly depressed (defined as an IDS-C score more than 24; Rush et al., 1996) over the previous month were assessed for safety, paid and sent home with no further procedures administered. These participants were given opportunity to re-enroll in the study once symptoms returned to inter-episode level. Only participants who remained inter-episode throughout the one-month study period were included in the analyses. Measurement periods did not include Daylight Savings time shifts or trips requiring changes in time zone.

### **Data analytic strategy**

Morningness/eveningness scores were calculated using the CS and the inter-episode BD and healthy control groups were compared using independent samples t-tests. Sleep timing variables (including 'Sleep onset time,' 'Morning wake time,' and 'Midsleep,') were estimated both subjectively via daily diary and objectively via actigraphy. When examining 'Sleep onset time,' 'Morning wake time,' and 'Midsleep,' standard clock times were converted into variables representing the number of minutes from midnight. This allowed accurate calculations of means and standard deviations (these values have been translated back to clock time in the results section and table 2 for ease of viewing). Instability in sleep and wake timing 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). In order to test differences in sleep timing variables between the inter-episode BD and healthy control groups, independent samples t-tests were used.

Prior to analyzing circadian activity, the actiwatch data was first scanned for missing data. Time limits were set for the 4-week period. The file was reviewed, and the intervals were individually set for each day and night period using, in order of priority as decision guides, the event marker, diary data, and Actiware software (version 5.5, Respironics Inc., Seattle, WA). To determine circadian rhythms, cosinor analysis fits a cosine and sine wave to the wrist actigraphy data using a 2-level linear mixed-effects cosinor regression model. A fixed 24-hour pattern is fit to the data, and then the midline estimating statistic of rhythm (MESOR; 24-hour adjusted mean value or y-intercept), the amplitude (half the peak-to-trough difference), and acrophase (time of day for peak activity), were calculated for each individual. The mixed model included a random intercept to account for inter-individual differences in overall activity. Model 1 analyzed activity as a continuous dependent variable with only cosine and sine terms entered as predictors and random effects at the subject level with unstructured covariance. In model 2, a dummy coded variable for bipolar disorder group status was added to model 1 to evaluate group differences in the circadian parameters. Model 3 added a dummy coded variable for CLOCK (CT vs. TT) genes to model 2, and model 4 added a dummy coded variable for the PER3 gene (4r/4r vs. 4r/5r vs. 5r/5r) to model 2. SPSS (version 19, IBM, Inc., Chicago, IL) was used for all statistical analyses.

## Results

### Participant Characteristics and Chronotype

Demographic characteristics and the baseline clinical data for participants are presented in Table 1. CS defined chronotype is also presented at the end of Table 1. The bipolar and control groups did not differ significantly in age, gender, race/ethnicity, annual household income, or employment status. The groups differed with respect to marital status (a greater proportion of controls were married or cohabiting with a partner). 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). The average Somatotherapy Index score in the bipolar group was low. No control group participants were taking psychotropic medications.

Bipolar participants obtained lower scores than controls on the CS, indicating that bipolar participants exhibit more “eveningness” relative to controls. However this difference was not statistically significant,  $t(71) = 1.09$ , *ns*; see Table 1. When CS was analyzed as a categorical variable (top 25% categorized as “morning-types”; middle 50% categorized as “Intermediates”; bottom 25% categorized as “evening-types”), there was a trend for group differences such that there are more “Intermediates” in the control group,  $\chi^2 = 5.48$ ,  $p = 0.06$ . Mania symptom severity at baseline was significantly correlated with CS score,  $r = -.37$ ,  $p < .01$ ,  $n = 70$ , in both the bipolar group,  $r = -.36$ ,  $p < .05$ ,  $n = 34$  and control group,  $r = -.33$ ,  $p = .05$ ,  $n = 36$ . Depression symptom severity and medication levels were not correlated with CS score.

### Sleep timing and sleep timing instability

Table 2 presents the means and stability values for both the actigraphic and sleep diary measurements of sleep onset time, morning wake time and midsleep for the bipolar and control groups. As measured by actigraphy, bipolar participants exhibited significantly more instability in morning wake time relative to controls ( $t(67) = 2.37$ ,  $p < 0.05$ ). As measured by diary, bipolar participants exhibited significantly more instability in midsleep than controls ( $t(67) = 2.26$ ,  $p < 0.05$ ). There were no significant group differences in mean level or instability of sleep onset time as measured by both actigraphy and sleep diary. Furthermore, there were no significant group differences in mean level or instability of morning wake time as measured by sleep diary or midsleep as measured by actigraphy. The effect sizes for all of the instability variables revealed large effects ( $d > 1.4$ ) for differences between the groups. In order to examine the effect that daytime employment has on sleep timing variables, two groups were created; Scheduled work (including full-time and part-time) and Unscheduled work (including unemployed and students). The same stability variables (actigraphy morning wake time and sleep diary midsleep) remained significantly more variable in the bipolar group in both the Scheduled work ( $ts(42) = 2.32$  and  $2.26$ , respectively,  $ps < 0.05$ ) and Unscheduled work ( $ts(28) = 2.59$  and  $2.38$ , respectively,  $ps < 0.05$ ) groups. Baseline symptom severity and medication levels were not correlated with any of the sleep timing variables.

## Circadian Cosinor Analysis

Table 3 displays the coefficients of the models of circadian modulation of activity. Model 1 revealed that the cosinor model has a significant circadian modulation in activity with midline estimating statistic of rhythm (MESOR) equal to 243.64 G, an amplitude of 1.19 G, and an acrophase at 21:07h. Model 2 compared circadian modulation in activity between the bipolar and control groups. There were no significant differences between the groups on MESOR, amplitude or acrophase.

For Model 3, participants were compared based on bipolar group status and CLOCK gene dummy code. There was a trend for group differences in the bipolar group, such that bipolar participants who were TT homozygotes had lower MESOR activity relative to bipolar participants with a C-allele and the controls (coef = 12.73,  $p = 0.07$ ). There were no group differences in amplitude or acrophase. Model 4 compared participants based on bipolar group status and PER3 gene code. There were no significant group differences in MESOR, amplitude or acrophase. When all models were adjusted for demographic variables including age, gender, race/ethnicity and household income, gender emerged as a significant predictor of amplitude in all models such that females had significantly higher amplitude (coef = 0.07,  $p = 0.001$ ). However, this did not change the statistical significance for any other predictors. Baseline symptom severity and medication levels were not correlated with any of the circadian activity variables.

## Discussion

The present study sought to extend and clarify the literature on circadian rhythms and sleep timing in inter-episode BD. This is an important gap in knowledge given that the majority of previous research suggesting circadian rhythm abnormalities in BD has been conducted on individuals in a manic or depressed episode. Moreover, when the focus has been on the inter-episode period, methods of data collection and analysis have varied widely and observation periods have been short (7 days or less). Additionally, previous studies have rarely made a distinction between the homeostatic sleep system, the circadian system, and the behaviors related to both, making results difficult to interpret. The current analyses sought to contribute to addressing these discrepancies and uncertainties through a multimethod approach to measurement and analysis over a one-month period.

Before moving onto a discussion of the results, two limitations are pertinent. First, the data analysis for the sleep timing variables required multiple comparisons. As such, there is concern about Type I error. We considered reducing the number of multiple comparisons by collapsing variables into larger categories. However, we decided against this option as our goal was to shed light on conflicting results in the literature so as to guide future research. As Nakagawa (2004) suggests, multiple comparisons increase the chance of a type I error, however, adopting more conservative error rates increases the chance of type II errors. We suggest the potential for deriving novel hypotheses is best done by providing maximal detail in the results and is diminished by collapsing into larger categories. Second, the sample size of the current study is small. Future research is needed with larger samples, particularly for the genetic analyses (Duncan & Keller, 2011).

Moving to a discussion of the key findings, our first aim was to use a psychometrically validated questionnaire to examine differences in chronotype between inter-episode BD and

healthy controls. This hypothesis was not fully supported. There was a trend for significance, such that BD participants were slightly more likely than controls to be an evening chronotype. Previous reports of eveningness in BD (e.g., Mansour et al., 2005) have not examined chronotype in an inter-episode BD group. Although reported chronotype has previously been regarded as a trait (e.g., Smith et al., 1989), recent evidence suggests that chronotype may be mood-state dependent in BD samples (Wood et al., 2009) and the general population (Chelminski et al., 1999). Indeed, in our analysis, we found an association between the severity of manic symptoms and eveningness in both the bipolar and control groups. This finding suggests that even among BD individuals who were strictly inter-episode, low levels of symptoms may influence reported chronotype. Future longitudinal studies are required to examine changes in chronotype across illness episodes.

The second aim was to examine, over a one-month period using sleep diary and actigraphy, the instability of sleep timing in inter-episode BD compared to healthy controls. Consistent with our hypothesis, the BD group exhibited more instability in wake-up time (via actigraphy) and reported more instability in midsleep (via sleep diary). Moreover, the large effect sizes for all of the instability measures in sleep timing suggest that the BD group has more difficulty keeping consistent sleep schedules. Note that, when the effect of employment status was examined, BD group status continued to be a significant predictor of unstable sleep timing. These results augment previous work highlighting disturbed sleep in inter-episode BD (e.g., Harvey et al., 2005; Talbot et al., 2009) and further suggest that instability in sleep timing may contribute to poor sleep. Instability in sleep timing will be an important target for treatment planning in BD and interventions aimed at encouraging consistent sleep patterns are already being developed and tested (Frank et al., 2008; Harvey et al., 2012; Kaplan & Harvey, 2012).

The third aim was to examine, over a one-month period via actigraphy, the differences in circadian modulation of activity in inter-episode BD relative to controls. Inconsistent with our hypotheses, there were no differences between the groups in mean circadian activity (referred to as MESOR), peak circadian activity (amplitude) or phase of circadian activity (acrophase). This result appears to be in contrast to previous reports (e.g., Jones et al., 2005; Salvatore et al., 2008). However, while recognizing the strengths of the current analysis (i.e., longer measurement period, more precise cosinor analysis, strict inter-episode cut-offs), our findings do not lend support to the hypothesis that circadian rhythm abnormalities are enduring trait-like features in inter-episode BD. Coupled with the findings on instability of sleep timing, it is possible that the sleep-related behaviors (e.g., consistency of bedtime and waketime) rather than endogenous circadian rhythm abnormalities of individuals with BD are contributing to disturbed sleep (see Benca et al., 2009 for review). Although there are ethical concerns with the use of forced desynchronization (Dijk & Cajochen, 1997) and constant routine protocols (Monk, Buysse, Frank, Kupfer, Dettling & Ritenour, 1994) when studying circadian rhythms in BD (Harvey, Murray, Chandler, & Soehner, 2010), innovative methods are needed to tease out the relative contributions of behavior versus the endogenous circadian rhythm. If replicated, these results have encouraging implications for treatment development research, given that behavior is modifiable.

The final aim was to examine the influence of two clock genes (CLOCK and PER3) on circadian modulation of activity over a one-month period in inter-episode BD relative to the control group. Similar to previous reports of inter-episode BD (Benedetti et al., 2007), we found no differences in MESOR, amplitude or acrophase between the different genotype groups. There was a trend for overall lower MESOR in BD participants who were carriers of the C-allele of the

CLOCK gene and it is possible that with a larger sample, this result may have reached statistical significance. Indeed, current recommendations for the study of cGxE interactions suggest using very large samples to find reliable significant results (see Duncan & Keller, 2011 for review). Also, it is clear that complex behavior will not be explained by single genes. Rather, it is possible that BD and circadian rhythm abnormalities are the result of multiple gene interactions with the environment (e.g., Shi et al., 2008) or that gene expression is disturbed rather than DNA (Yang et al., 2009). However, it is important to note that previous studies have not examined the influence that circadian genes have on behavior. Indeed, many resources have been spent with a focus on Genome wide association studies (GWAS) in BD, but unfortunately these studies have led to disappointing results that are not replicated (Baum et al., 2008). Most likely BD is made up of many genetic risk alleles that all make a very small contribution towards the development and maintenance of BD.

Interestingly and importantly, many of the medications used to treat BD are known to regulate circadian rhythms. Even in the animal literature, mice exhibiting manic symptoms due to clock gene abnormalities have their symptoms effectively treated by lithium or other circadian regulating agents (Roybal et al., 2007; Mohawk et al., 2009). All of the BD participants in the current study were in the care of a psychiatrist prescribing medication and many were also involved in psychosocial treatments. Medication levels were not correlated with circadian modulation of activity via MESOR, amplitude and acrophase in the current analysis. However, the BD participants were taking a heterogeneous group of medications and most (20 of 35) were taking more than one medication, potentially creating unknown interaction effects. Combined with a small sample, the heterogeneity of medication use precluded analysis by individual or subgroups of medication. It is also important to note that psychosocial treatments our participants may have received may also have impacted regulation of their circadian rhythms. Indeed, there is evidence to suggest that psychosocial treatments targeting daily activity schedules (including sleep, meal times, bright-light, etc.) work to minimize symptomatology by regulating circadian rhythms (Frank et al., 2008).

The method of measurement - self-report versus objective estimate – provided converging levels of analysis. Differences in sleep timing were observed using both sleep diary and actigraphy. However, there remained a lack of consistency between the two measures. Lack of coherence in subjective versus objective measures have been of interest across multiple fields. For example, research on sleep has yielded interesting findings regarding the discrepancy between subjectively reported wake time and objective measures of wake time such as actigraphy and polysomnography in bipolar disorder (Harvey, et al., 2005; Talbot, et al., 2009; Gershon, et al., in press). Several resolutions to the lack of coherence between subjective and objective measures of sleep have been proposed (Harvey & Tang, 2012). One possibility is that subjective perception may be more sensitive to sleep disturbances than the objective methods currently used to measure sleep. Actigraphy defined sleep onset begins with the first phase of inactivity. Good sleepers pass through inactivity into sleep onset quickly while poor sleepers are known to move through this phase of inactivity to sleep onset more slowly (Tyron, 2004). This raises the possibility that poor sleepers may be more reliable at estimating sleep onset than actigraphy. This may be a particularly important line of inquiry for those researchers and clinicians interested in studying and promoting consistent sleep schedules.

In conclusion, while the current results did not support the hypothesis that endogenous circadian rhythm abnormalities are an enduring trait-like feature in inter-episode BD, the results highlighted the importance of instability in sleep timing as an important and modifiable feature



of inter-episode BD. This study raises several critical domains for future research. First, we emphasize that the circadian ‘proxies’ measured in the present study have limitations and that there is a need to tease apart the relative contributions of behavior and the endogenous circadian clock. Second, more research is needed with larger samples to adequately estimate the effect that clock genes play in the maintenance of BD. Third, future research using longitudinal within-subject studies are needed to clarify the role of circadian rhythms across phases of bipolar illness, taking into account the role of treatments that stabilize circadian rhythms.

Table 1

<b>Demographic Characteristics and Baseline Clinical and Chronotype Data</b>			
	Bipolar Participants ( <i>n</i> = 35)	Control Participants ( <i>n</i> = 37)	Statistical difference values
Mean age in years (SD)	34.7 (10.5)	33.3 (12.6)	$t = .492, p = .624$
Gender			$\chi^2(1) = 1.01, p = .315$
Male	12	17	
Female	23	20	
Race/Ethnicity (N)			$\chi^2(5) = 7.00, p = .136$
African American	3	2	
Asian	3	12	
Hispanic	3	7	
Native American	1	0	
Caucasian	23	16	
Biracial/Other	2	0	
Marital Status (N)			$\chi^2(2) = 13.62, p = .018$
Single	25	20	
Married/Live-in partner	1	14	
Divorced/separated/widowed	9	3	
Annual Household Income <sup>a</sup> (N)			$\chi^2(4) = 4.77, p = .445$
Less than \$25,000	10	12	
\$25,000-50,000	15	14	
\$50,000-75,000	2	5	
\$75,000-100,000	5	2	
Over \$100,000	3	2	
Employment Status (N)			$\chi^2(3) = 1.40, p = .705$
Full-time	10	15	
Part-time	10	8	
Unemployed/Retired	9	7	
Student	6	7	
Mean Symptom Values (SD)			
Depressive Symptoms (IDS-C) <sup>b</sup>	8.8 (4.7)	2.3 (1.9)	$t = 7.63, p < .001$
Manic Symptoms (YMRS) <sup>b</sup>	3.1 (2.7)	.9 (2.0)	$t = 4.3, p < .001$

Mean Somatotherapy Index Score (SD)	1.8 (1.4)	--	
Means and Chronotype Category from Composite Scale Questionnaire (CS) <sup>c</sup>			
Overall Score (SD)	34.3 (9.5)	36.4 (7.1)	$t = 1.09, p = .281$
Evening-type (N)	12	6	$\chi^2(3) = 5.48, p = .065$
Intermediate (N)	12	24	
Morning-type (N)	8	6	

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*Note.* <sup>a</sup>Two control group cases missing annual household income. <sup>b</sup>One control group case missing depressive and manic symptom scores. IDS-C = Inventory of Depressive Symptomatology – Clinician Rating; YMRS = Young Mania Rating Scale. <sup>c</sup>One bipolar group case and one control group case were missing CS scores.

Table 2

**Means and Instability of Sleep Onset Time, Morning Wake Time and Midsleep for Bipolar and Control Participants**

	Group		T-tests
	Bipolar ( <i>n</i> = 32)	Control ( <i>n</i> = 36)	
Means of actigraphic sleep variables (SD)			
Sleep onset time (minutes)	12:34 (90.6)	12:46 (74.6)	0.60, <i>p</i> = .551
Morning wake time (minutes)	08:31 (99.2)	08:09 (70.6)	1.07, <i>p</i> = .289
Midsleep (minutes)	04:32 (89.4)	04:25 (70.3)	0.39, <i>p</i> = .701
Instability of actigraphic sleep variables in MSSD (SE)			
Sleep onset time	13155.6 (1616.7)	9413.2 (1289.5)	1.83, <i>p</i> = .072
Morning wake time	14780.8 (1631.1)	10009.3 (1221.5)	2.37, <i>p</i> = .021*
Midsleep	8484.62 (892.6)	6394.7 (764.5)	1.79, <i>p</i> = .078
Means of subjective sleep variables (SD)			
Sleep onset time (minutes)	12:18 (89.0)	12:37 (71.8)	1.00, <i>p</i> = .323
Morning wake time (minutes)	08:23 (93.2)	08:07 (70.5)	0.77, <i>p</i> = .444
Midsleep (minutes)	04:28 (85.6)	04:25 (69.4)	0.13, <i>p</i> = .898
Instability of subjective sleep variables in MSSD (SE)			
Sleep onset time	11605.9 (1636.8)	8199.4 (1017.3)	1.81, <i>p</i> = .075
Morning wake time	11974.9 (1596.3)	8399.2 (1132.3)	1.86, <i>p</i> = .068
Midsleep	7696.7 (995.15)	5228.6 (526.0)	2.26, <i>p</i> = .027*

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

Table 3

**Means of Circadian Modulation of Activity from Cosinor Analysis Models**

Model	Group	MESOR (SE)	Amplitude (SE)	Acrophase (SE)
1	Combined groups	243.64 (7.53)	1.19 (0.02)	21:07 (0:14)
2	Bipolar (N=35)	243.31 (8.76)	1.20 (0.02)	21:14 (0:24)
	Control (N=37)	247.58 (8.57)	1.18 (0.04)	20:57 (0:20)
3*	Bipolar CLOCK TT (N=19 of 33)	220.20 (8.93)†	1.18 (0.02)	21:06 (0:29)
	Bipolar CLOCK CT (N=11 of 17)	232.21 (6.76)	1.19 (0.03)	21:12 (0:28)
4*	Bipolar PER3 4r/4r (N=14 of 25)	237.44 (9.15)	1.14 (0.03)	19:57 (0:27)
	Bipolar PER3 4r/5r (N=12 of 21)	241.34 (9.62)	1.16 (0.04)	20:24 (0:24)
	Bipolar PER3 5r/5r (N=2 of 3)	245.24 (9.70)	1.18 (0.05)	20:57 (0:31)

MESOR = Midline estimating statistic of rhythm. \* Both Bipolar and Control were entered into the models, but only bipolar coefficients are displayed here. †  $p < 0.10$  using two-s

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