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Daytime Midpoint as a Digital Biomarker for Chronotype in Bipolar Disorder

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Abstract

Background: Bipolar disorder (BD) is associated with later sleep and daily activity (evening rather than morning chronotype). Objective chronotype identification (e.g., based on actigraphs/smartphones) has potential utility, but to date, chronotype has mostly been assessed by questionnaires. Given the ubiquity of accelerometer-based devices (e.g. actigraphs/smartphones) worn/used during daytime and tendency to recharge rather than wear at night, we assessed chronotype using daytime (rather than sleep) interval midpoints.

Methods: Sixty-one participants with BD type I (BD-I) or II (BD-II) and 61 healthy controls completed 25–50 days of continuous actigraphy. The Composite Scale of Morningness (CSM) was completed by a subset of this group. Daytime activity midpoint was calculated for each daytime

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Contributions

Dr. Kaufmann contributed to the research, data analysis, and writing of the manuscript. Drs. Gershon, Depp, Miller, Zeitzer, and Ketter, contributed to the data analysis and writing of the manuscript. All authors have approved the final article. The funding sources had no role in study design, analysis, and preparation of manuscript.

Conflicts of Interests

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interval, excluding naps. Evening chronotype was defined as having a daytime interval midpoint at or after 16:15:00 (4:15:00 PM).

Results: BD versus controls had delayed daytime midpoint (mean±standard deviation) (16:49:07±01:26:19 versus 16:12:51±01:02:14, $p<0.01$), and greater midpoint variability (73.3±33.9 minutes versus 58.1±18.3 minutes, $p<0.01$). Stratifying by gender and age, females and adolescents with BD had delayed and more variable daytime midpoints versus controls. Adults with BD had greater midpoint variability than controls. Within-person mean and standard deviations of daytime midpoints were highly correlated with sleep midpoints ($r=0.99$, $p<0.001$ and $r=0.86$, $p<0.001$, respectively). Daytime midpoint mean was also significantly correlated with the CSM ($r=-0.56$, $p<0.01$).

Limitations: Small sample size; analyses not fully accounting for daytime napping.

Conclusions: Wrist actigraphy for determination of daytime midpoints is a potential tool to identify objective chronotype. Exploration of the use of consumer devices (wearables/smartphones) is needed.

Keywords

Bipolar Disorder; Chronotype; Daytime; Actigraphy

INTRODUCTION

Sleep disturbance is a pervasive and persistent phenomenon in bipolar disorder (BD), experienced by between 70–99% of BD patients (Harvey, Talbot, & Gershon, 2009). Abnormalities in sleep quality, as well as circadian rhythm irregularities, may be markers of current or imminent manic or depressive episodes (Cretu, Culver, Goffin, Shah, & Ketter, 2016; Gershon et al., 2017; Perlman, Johnson, & Mellman, 2006), or future positive or negative affect (Kaufmann, Gershon, Eyler, & Depp, 2016), and therefore are important markers for monitoring BD course and treatment progress. In recognition of the importance of sleep and circadian rhythms for illness course and treatment, managing sleep and circadian rhythm irregularities in BD care has been a key target of therapeutic efforts—therapies such as Interpersonal and Social Rhythm Therapy (Ehlers, Frank, & Kupfer, 1988; Frank, Swartz, & Kupfer, 2000) designed to stabilize circadian patterns, may thus mitigate mood fluctuations (Frank, Swartz, & Boland, 2007).

Accurately identifying chronotype (i.e., eveningness or morningness preference) in BD patients could importantly enhance the efficiency of allocating appropriate therapeutic interventions. Traditionally, clinicians and researchers alike have relied upon self-report instruments (for example, the Horne-Östberg Morningness-Eveningness Questionnaire (MEQ) (Horne & Östberg, 1976), the Composite Scale of Morningness (CSM) (C. S. Smith, Reilly, & Midkiff, 1989), and the Munich Chronotype Questionnaire (MCTQ) (Roenneberg et al., 2007)), to identify chronotypes. Such categorizations have proven useful, have shown good psychometric properties (C. S. Smith et al., 1989; Zavada, Gordijn, Beersma, Daan, & Roenneberg, 2005), and have commonly found BD associated with greater eveningness (rather than morningness) chronotype relative to control groups (Melo, Abreu, Linhares Neto, de Bruin, & de Bruin, 2017).

Given the circadian rhythm irregularities inherent in BD, objective chronotype measurement could prove useful in providing enhanced chronotype data on a night-to-night basis. For example, wrist actigraphy, a common tool used to estimate sleep/wake patterns in sleep research, could characterize individual nights of sleep, and thus identify emerging changes in sleep timing patterns and in next-day emotional affect, incident mood episodes and other clinically important emergent psychiatric events, such as hospitalization. This could provide clinically useful additional information, beyond overall categorical classifications of morningness/eveningness. We recently published work investigating the utility of examining objective sleep interval midpoint values (based on wrist actigraphy) as a possible chronotype index, and its correlation with subjective chronotype (as measured by the CSM) (Gershon et al., 2018). We found objective (actigraphy-derived) sleep interval midpoint values yielded reliable estimates comparable to self-reported chronotype.

In our previous study, we assessed chronotypes based on objectively measured sleep intervals (e.g., in-bed vs. out-of-bed). However, assessing midpoints based on non-sleep (daytime) activity intervals (e.g., out-of-bed vs. in-bed) may also prove clinically useful, with applications to large-scale studies using new wearable (e.g. actigraphs) and non-wearable (e.g. smartphones) commercial devices that contain accelerometers and are used primarily during the day, and recharged rather than used at night. Given daytime intervals might be longer than sleep-intervals, their midpoint values may be more variable providing more information about intermediate types. Indeed, with the recent rapid increase in smartphone ownership (A. Smith, 2013), researchers and industry alike have sought to identify ways to harvest passively collected device data (e.g., call logs, accelerometer data, texts, screen-on time) to inform health outcomes, including psychiatric conditions (Institute of Electrical and Electronics Engineers.; J. Torous, Kiang, Lorme, & Onnela, 2016; J. Torous, Staples, & Onnela, 2015), and of relevance to this study, BD (John Torous & Powell, 2015).

While out-of-bed versus sleep intervals may not always be directly available through passive data collection on smartphones, such intervals may be estimated, based on phone activity and phone metadata (e.g., screen power on and charging times) throughout the day. For example, using data from the National Health and Nutrition Examination Survey (which collects physical activity data using accelerometers worn during the day), Urbanek et al. found that among 11,951 participants, accelerometer wear times and their associated sleep interval midpoints yielded chronotypes similar to self-reported chronotypes (Urbanek et al., 2017). In BD, identifying accurate chronotype may help support activity based social rhythm interventions, such as Interpersonal and Social Rhythm Therapy (Ehlers et al., 1988; Frank et al., 2000) resulting in highly personalized BD management.

In this study, we extended findings from our previous study examining chronotypes based on nighttime objective activity during sleep intervals to see if analogous (daytime) non-sleep interval chronotypes could be derived from objective activity. The specific purpose of this study was to assess daytime interval midpoint values in BD relative to healthy control participants and compare these results to our previous sleep interval midpoint values, as reported elsewhere (Gershon et al., 2018). We hypothesized BD patients would have significantly later daytime midpoints than controls (indicating eveningness chronotype), and

that daytime midpoints would be correlated with sleep midpoints for both BD and healthy control participants.

METHODS

Participants

Participants were drawn from two studies. The first study (conducted from 2007–2010 at UC Berkeley [Berkeley, CA]) consisted of a community-recruited sample of 76 adults (ages 18–64 years): 36 adults with inter-episode (no syndromal episode for a least 1 month) BD type I (BD-I) or II (BD-II) and 40 adult healthy controls with no history of psychiatric or sleep disorder. The second study (conducted from 2014–2018 at Stanford University [Stanford, CA]), consisted of a community-recruited sample of 46 adolescents and young adults (ages 14–21 years): 25 with inter-episode (no syndromal episode for a least 1 month) BD-I or BD-II and 21 healthy controls with no history of psychiatric or sleep disorder. In both studies, we recruited participants residing in the San Francisco Bay Area using online advertisements and flyers posted in the community and clinics. As study 2 included adolescents, subjects were also recruited through advertisements in local colleges and high schools, and at clinics/organizations serving youth with mental illness. Study exclusion criteria included the presence of serious medical or neurological condition (e.g., Alzheimer's disease, history of severe head trauma), alcohol or substance abuse or dependence in the past six months, shift work, an unstable living arrangement, or a primary sleep disorder (e.g., sleep apnea). Participants in the BD group were required to (1) meet diagnostic criteria for BD-I or BD-II according to the Structured Clinical Interview for DSM (SCID; First, Spitzer, Gibbon, & Williams, 2007), or for youths under age 18 years, the Kiddie Schedule of Affective Disorders and Schizophrenia (K-SADS; Kaufman et al., 1997), (2) be under psychiatric care, and (3) exhibit inter-episode status at study entry. Inter-episode status was defined as the absence of a syndromal depressive, (hypo)manic, or mixed episode in the preceding month (as assessed by the SCID) and scoring at or below mild symptom levels on the Clinician Rated Inventory of Depressive Symptomatology (IDS-C; score ≤ 23 ; Rush, Gullion, Basco, Jarrett, & Trivedi, 1996) or, for youth under the age 18 years, the Children's Depression Rating Scale (CDRS; score ≤ 30 ; Poznanski, Mokros, Grossman, & Freeman, 1985) as well as the Young Mania Rating Scale (YMRS; score ≤ 11 ; Young, Biggs, Ziegler, & Meyer, 1978). Participants in the control group were required to show no evidence of any current or lifetime Axis I psychiatric disorder according to the SCID or K-SADS. See Supplemental Figure 1 for flow diagram of study recruitment. Subjects were compensated for participation (up to \$150 for study 1 and up to \$215 for study 2).

Procedure

The University of California's Committee for the Protection of Human Participants and Stanford University's Administrative Panel on Human Participants Research approved this research. Written informed consent was obtained prior to participation in protocol activities. For youths under age 18 years, we obtained assent with written informed consent from a legal guardian. Eligible participants were administered in-person diagnostic interviews to assess lifetime psychiatric disorders (SCID or K-SADS, for youths under age 18 years) and current mood symptom levels (YMRS and the IDS-C or CDRS, for youths under age 18

years), and completed questionnaires to assess demographic and clinical characteristics and current medication use. In the first study, the diagnostic and symptom interviews were administered by A.G. or by trained clinical psychology doctoral graduate students, and in the second study the diagnostic and symptom interviews were administered by A.G. In total, the visit duration for each study was approximately 3–4 hours. Participants wore an actigraph, a watch-like activity-monitoring device, continuously on the non-dominant wrist for approximately eight weeks in the first study and for approximately three weeks in the second study. Brief daily sleep diaries were completed concomitant with actigraphy (each entry requiring no more than 10 minutes to complete). Most participants (N=111 out of 122) completed the Composite Scale of Morningness (CSM).

Measures

Lifetime Psychiatric Disorders.

Lifetime bipolar disorder and Axis-I comorbid psychiatric disorders were assessed using the above-mentioned structured diagnostic interviews. Thus, adult participants (18 years or older) were interviewed using the Structured Clinical Interview for DSM (SCID; First et al., 2007) whereas participants under age 18 years were interviewed using the Kiddie Schedule of Affective Disorders and Schizophrenia (K-SADS; Kaufman et al., 1997).

Current Mood Symptom Severity.

Current (past-month) depressive symptom severity was assessed using the Clinician-Rated Inventory of Depressive Symptomatology (IDS-C; Rush et al., 1996) for adults or the Children's Depression Rating Scale-Revised (CDRS-R; Poznanski et al., 1985) for youths under age 18 years. Current (past-month) mania symptom severity was assessed using the Young Mania Rating Scale (YMRS; Young et al., 1978).

Subjective Chronotype.

Participants completed the Composite Scale of Morningness (CSM; C. S. Smith et al., 1989), an instrument used to measure preference towards evening or mornings. Scores range from 13 to 55 with higher scores indicating greater preference towards mornings. The CSM has shown good psychometric properties (C. S. Smith et al., 1989; Tonetti, Adan, Di Milia, Randier, & Natale, 2015). Specifically, higher scores on CSM have been shown to be associated with self-reported morning activities (e.g., earlier contact with other people, earlier meals, and earlier work times) (Randier & Jankowski, 2014), and earlier sleep patterns as measured by wrist actigraphy (Thun et al., 2012).

Actigraphy.

Movement data were collected by Actiwatchs, specifically the AW64 model for study 1 and the Spectrum Pro model for study 2 (Respironics Inc., Bend OR). Actiwatchs are watch-like devices worn continuously on the wrist of the non-dominant hand and which record the vector magnitude of tri-axial movement within one-minute segments. Data were downloaded and visualized using Actiware software (v.5.5 for Study 1 and v.6.0.9 for Study 2; Respironics Inc., Bend OR), and scored by trained research assistants to identify non-sleep (versus sleep) intervals based on activity patterns and participant-completed sleep diaries.

In this paper, we focus on daytime (non-sleep) intervals, assessing intervals between when participants got out of bed to when participants went back to bed. In this report, we refer to these intervals as “daytime intervals.” Using scored output from Actiware software, we obtained out-of-bed and in-bed times based upon “major intervals” (excluding clear “minor intervals”; i.e., naps). If a sleep interval was not recorded (e.g., data for that night were excluded due to any reason, including equipment malfunction), we excluded that individual’s corresponding daytime interval. Similar to our methods described elsewhere (Gershon et al., 2018), we computed daytime and sleep interval midpoints based upon in-bed and out-of-bed times. In order to make midpoints comparable across days, we standardized each midpoint by assigning a value representing the number of seconds from midnight the previous day. For example, a midpoint of 2:00pm (14:00:00) would be assigned a value of 136,800 seconds. We translated these values to 24-hour clock times (hh:mm:ss) to facilitate interpretation.

Data Analysis

Our analyses were conducted in four stages. First, we compared demographic and clinical characteristics of BD and healthy control participants. Second, we compared within-person means and standard deviations of standardized daytime interval midpoint values between the BD and healthy control groups and tested for statistical significance using unpaired t-tests. These results were also stratified by gender and age (<18 years, 18+ years). Third, we calculated the proportion of each participant’s daytime intervals which were classified as evening type (defined as having activity midpoint occurring after 16:15:00) and based on percentage thresholds (i.e., 50.0%, 66.7%, 75%, 90.0%) calculated group differences for proportion classifying as evening/non-evening (including intermediate) types using Fisher exact tests. Finally, we assessed correlations between within-person mean and standard deviation of daytime interval midpoints and sleep interval midpoints (data for which were calculated in our previous study; Gershon et al., 2018) and computed Pearson correlations within the entire sample and within BD and healthy control groups separately.

RESULTS

Demographic and clinical characteristics were described in our previous report (see Table 1 in that publication) (Gershon et al., 2018). Briefly, BD and healthy control participants did not differ with respect to demographic characteristics (age, gender, race/ethnicity, education, and employment status). Mean age was 28.2 (SD = 11.5) years for BD group and 27.9 (SD = 13.6) for the healthy control group, and females comprised of 67.2% of those with BD and 50.8% of healthy controls. As expected, participants with BD, as compared to healthy controls, reported greater residual (i.e., subsyndromal) depressive (on both the IDS-C and CDRS) and manic (on the YMRS) symptoms. Specifically, participants with BD had a mean $\pm$ standard deviation IDS-C score of 8.6 ± 4.6 (range=0–23), CDRS-R score of 27.4 ± 7.7 (range=17–48), and YMRS score of 3.8 ± 3.4 (range=0–15).

Mean daytime interval midpoint for BD participants (16:49:07) was significantly later than for healthy controls (16:12:51) ($t_{(120)} = 2.66$; $p < 0.01$). Similar differences (e.g. midpoints for BDs vs. healthy controls) were observed in females as well as those <18 years old (Table

1). BD participants also exhibited greater variability in daytime midpoints relative to controls (average SD = 73.3 versus 58.1 minutes; $t_{(120)} = 3.09$; $p < 0.01$), with similar significant trends observed in female, adolescents, and adults (Table 2). Based upon evening chronotype thresholds of percentages of daytime interval midpoints occurring after 16:15:00, there was no statistically significant difference across study groups (Table 3).

Within-person mean daytime interval midpoints were highly significantly correlated with sleep interval midpoints among all participants ($r = 0.99$, $p < 0.01$, $N = 122$, Figure 1). Within-person SDs of daytime interval midpoints also significantly correlated with sleep interval midpoints ($r = 0.86$, $p < 0.01$, $N = 122$), albeit to a somewhat lesser degree, especially in controls (Figure 2). Thus, these patterns were seen among not only BDs (means: $r = 0.99$, $p < 0.01$; SDs: $r = 0.89$, $p < 0.01$; $N = 61$) but also healthy controls (means: $r = 0.99$, $p < 0.01$; SDs: $r = 0.72$, $p < 0.01$; $N = 61$). An example of differences in daytime and sleep interval midpoints is displayed in Figure 3. Daytime interval midpoint means also correlated significantly with CSM mean scores in the total sample ($r = -0.56$, $p < 0.01$), among BDs ($r = -0.62$, $p < 0.01$), and among healthy controls ($r = -0.42$, $p < 0.01$) separately.

DISCUSSION

Studies using self-reported chronotype suggest BD is associated with a preference for eveningness (Melo et al., 2017). Few studies have examined this preference using objective actigraphy-derived measurement (Gershon et al., 2018), and none have used daytime intervals rather than sleep intervals. The purpose of this study was to assess daytime interval midpoint values based on 25–50 days of continuous actigraphy, as a potential marker of chronotype, in BD participants relative to healthy controls, and to determine the correspondence between daytime interval midpoints and sleep interval midpoints as chronotype markers in BD and healthy controls. Consistent with our previous findings and those from other investigators (Gershon et al., 2018; Melo et al., 2017), BD participants showed significantly later and somewhat more variable daytime interval midpoints than did healthy controls. In addition, daytime interval midpoints were strongly correlated with nighttime (sleep) interval midpoints in both BD participants and healthy controls. In addition, daytime interval midpoint variability was significantly (though less strongly) correlated with sleep interval midpoint variability in both BD and controls. Taken together, our results indicate that using daytime interval midpoint values to measure chronotype may yield results similar to those obtained using sleep interval midpoint values.

Compared to sleep interval midpoints, the variability (SD) of daytime interval midpoints became less correlated as variability of midpoints increased, suggesting that caution should be used in the interpretation of data from persons with variable daytime interval midpoints. However, future studies are needed to explore our methods using larger samples and longer follow-up periods to assess whether there may be shifts in chronotypes over time and whether these shifts relate to clinically important changes, such as onset of syndromal depressive or manic episodes in BD.

Our findings suggest exciting possibilities for developing highly individualized clinical interventions for managing BD symptoms. Smartphone applications are already proving to be useful adjuncts to clinical care (Depp et al., 2010; Depp, Moore, Perivoliotis, & Granholm, 2016). As chronotype can be assessed on a night-to-night basis, machine learning algorithms could identify periods that are abnormal for individual patients and help triage such participants to appropriate interventions targeted for context, location, and time of day. Among smartphone data, other passively-collected indicators (e.g., texting, phone calls, and screen on time) may help inform early interventions for emerging clinical problems. While the usefulness of passively-collected data collected from mobile devices is still being assessed (Institute of Electrical and Electronics Engineers.; J. Torous et al., 2016; J. Torous et al., 2015) and their usefulness for chronotype assessment could vary based upon how mobile devices were used, future research needs to identify the best indicators for mood state shifts and other clinically important emergent events, such as hospitalization. More research is also needed to determine if such chronotype-related interventions may augment clinical treatment plans.

Several limitations of our research should be acknowledged. First, our sample size was relatively small, and mostly Caucasian and female. Replication with larger and more diverse samples is warranted. Second, among the BD group, we restricted participant eligibility to individuals who were inter-episode at study entry, and who remained relatively stable throughout the course of the prospective assessment period. In the first study (adult sample), participants were assessed for symptoms and functioning at monthly intervals during the eight-week course of the study. In the second study (adolescent and young adult sample), participants were assessed for symptoms and functioning only at baseline. As such, we could not test for the extent to which daytime interval midpoints predicted episode recurrence. Chronotype has been traditionally thought of as a relatively stable trait-like characteristic, although some data suggest that it may be related to illness severity (Mansour et al., 2005). It remains to be established whether or not transient chronotype shifts herald episodes of syndromal mania and/or depression in BD. Third, medication use may have had confounding effects on daytime midpoints. All but 7 (of 61) participants in the BD group reported currently taking prescription psychotropic medications relative to none of the control group participants. Fourth, among BD participants, 41 out of 61 had at least one lifetime comorbid Axis-I psychiatric diagnosis. There is some evidence to suggest that both anxiety disorders and substance abuse or dependence is associated with greater eveningness as well (Fares et al., 2015; Lemoine, Zawieja, & Ohayon, 2013; Reid et al., 2012), and thus we cannot be sure that the eveningness observed in our BD group was solely explainable by BD (as opposed to a comorbid diagnosis). Finally, our analyses did not account for naps. Actigraphy is not optimized to determine periods of napping and any periods that appeared to be consistent with napping were excluded from our analyses. It is uncertain the extent to which naps might have impacted chronotype classification. For example, individuals who slept mid-day may have had trouble falling asleep that night yielding a later than normal daytime interval midpoint.

Taken together, our study found that daytime interval midpoints can indeed be useful tools for chronotype classification. This has potential implications not only for monitoring sleep health in the general population, but also for providing highly targeted and personalized

early interventions to improve the treatment course of individuals with severe mental illnesses with sleep abnormalities such as in those with BD. Future research may seek to determine the utility of examining transient (day-to-day or night-to-night) chronotype changes and their associations with affective functioning and BD symptomatology, and apply this methodology to other clinical populations with other affective disorders/transient mood symptoms or other chronic diseases requiring self-management (e.g., diabetes). Utilizing this measure with large amounts of passively-collected data from smartphones also may help explore population trends informing public health interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Bipolar disorder (BD) associated with later chronotype
- We assessed daytime intervals from actigraphy as chronotype measures in BD
- BD patients had earlier/more variable daytime midpoints than healthy controls
- Daytime midpoints correlated with nighttime midpoints and subjective chronotype

Figure 1. Correlations Between Within-Person Daytime and Sleep Interval Midpoint Means Across Whole Sample.

Note: Time format is hh:mm. Daytime interval midpoint means calculated across all daytime intervals per-person. Sleep interval midpoint means calculated across all sleep intervals per-person. Dashed green line corresponds to line of unity. Red solid line corresponds to regression line. Shaded range corresponds to 95% confidence interval. Regression equation: $y = 42478.15 + 1.01 \cdot x$; $r = 0.99$, $p < 0.01$.

Figure 2. Correlations Between Within-Person Daytime and Sleep Interval Midpoint Variability (SD) in Minutes Across Whole Sample.

Note: Daytime interval midpoint standard deviations (SDs) calculated across all daytime intervals per-person. Sleep interval midpoint standard deviations (SDs) calculated across all sleep intervals per-person. Dashed green line corresponds to line of unity. Red solid line corresponds to regression line. Shaded range corresponds to 95% confidence interval. Regression equation: $y=497.67 + 0.76 \cdot x$; $r=0.86$, $p<0.01$.

Figure 3. Example of Sleep & Daytime Intervals & Corresponding Midpoint Means for a Participant with Bipolar Disorder.

Note: Vertical red lines represent thresholds for eveningness time (i.e., 04:15:00 for sleep intervals, 16:15:00 for daytime intervals). Rows of markers correspond to consecutive sleep/daytime intervals. Sleep intervals: Mean midpoint=06:09:29, SD=98.8 minutes. Daytime intervals: Mean midpoint=18:18:12, SD=88.0 minutes.

Table 1.

Group Differences in Daytime Interval Midpoint Means

	Bipolar Disorder <i>n</i>=61 Time (SD)	Healthy Controls <i>n</i>=61 Time (SD)	<i>t</i>	p-value
All Participants	16:49:07 (01:26:19)	16:12:51 (01:02:14)	2.66	<0.01
Gender				
Female	16:44:43 (01:14:32)	16:00:14 (00:54:25)	2.80	<0.01
Male	16:58:08 (01:48:12)	16:25:54 (01:07:52)	1.30	0.20
Age				
<18 years	16:21:25 (00:54:53)	15:45:31 (00:30:26)	2.31	0.03
18 years	16:55:54 (01:31:34)	16:24:18 (01:08:36)	1.85	0.07

Note: Time format is hh:mm:ss. Daytime interval midpoint means calculated across all daytime intervals per-person, then per group. Group differences assessed using t-tests with raw seconds data. Significance threshold set at 0.05, with no correction for multiple comparisons.

Table 2.

Group Differences in Daytime Interval Midpoint Standard Deviations (SDs)

	Bipolar Disorder <i>n</i>=61 Minutes (SD of SD)	Healthy Controls <i>n</i>=61 Minutes (SD of SD)	<i>t</i>	p-value
All Participants	73.3 (33.9)	58.1 (18.3)	3.09	<0.01
Gender				
Female	72.6 (23.9)	57.1 (18.4)	2.98	<0.01
Male	75.0 (49.1)	59.1 (18.4)	1.61	0.11
Age				
<18 years	77.5 (27.2)	60.6 (15.1)	2.19	0.04
18 years	72.3 (35.5)	57.1 (19.6)	2.50	0.01

Note: Daytime interval midpoint standard deviations (SDs) calculated across all daytime intervals per-person, then per group. Group differences assessed using t-tests with raw seconds data. Significance threshold set at 0.05, with no correction for multiple comparisons.

Table 3.

Group Differences in Proportions of Participants Classified with Evening Chronotype, Based Upon Percent of Daytime Intervals with Midpoints After 16:15:00.

	Bipolar Disorder n=61	Healthy Controls n=61	<i>p</i>-value
50.0% of midpoints after 16:15:00, n (%)	34 (55.7)	25 (41.0)	0.15
66.7% of midpoints after 16:15:00, n (%)	28 (45.9)	19 (31.2)	0.14
75.0% of midpoints after 16:15:00, n (%)	25 (41.0)	16 (26.2)	0.13
90.0% of midpoints after 16:15:00, n (%)	14 (23.0)	6 (9.8)	0.09

Note: *p*-value comes from Fisher exact tests. Significance threshold set at 0.05.