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Social rhythm regularity and the onset of affective episodes in bipolar spectrum individuals

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Objectives: Research suggests that bipolar disorder individuals may have less social rhythm regularity than normal controls and that this may contribute to their affective symptoms and episodes. This study examined whether regularity prospectively predicted time to onset of major depressive, hypomanic and manic episodes in a sample with bipolar spectrum disorders.

Methods: We recruited 414 undergraduate students from Temple University and University of Wisconsin diagnosed with cyclothymia, bipolar II disorder, or with no affective disorder (normal controls). Participants completed the Social Rhythm Metric at Time 1 and structured interviews approximately every four months for an average follow-up period of 33 months.

Results: Participants diagnosed with cyclothymia and bipolar II disorder reported significantly fewer regular activities than normal controls, and approximately half of these participants experienced a worsening course of their illness over the study duration. Survival analyses indicated that both diagnosis and social rhythm regularity significantly predicted the time to participants' first prospective onset of major depressive, hypomanic and manic episodes.

Conclusion: Consistent with the social zeitgeber theory, bipolar spectrum participants reported less social rhythm regularity than normal controls, which prospectively predicted the survival time to affective episodes.

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Despite its public health significance, bipolar disorder has been understudied compared to other mental health disorders (1). Research suggests that disruptions of internal biological rhythms may be responsible for the affective shifts experienced by bipolar disorder individuals. For example, changes in the sleep-wake cycle, the most recognizable circadian rhythm, have been linked to affective episode onset (2, 3).

Social zeitgebers, or social cues, have been found to be as powerful in entraining circadian rhythms as natural zeitgebers such as light (4). Examples of social zeitgebers include daily activities such as meals, meetings, and exercise. Ehlers et al. (5) suggested a social zeitgeber theory for major depression that has subsequently been applied to the onset of mania. They proposed that life events result in changes in social zeitgebers, which, in turn, affect social rhythms and biological rhythms. Changes in time cues that promote stability may result in affective episodes among vulnerable individuals. Indeed, studies have linked the onset of affective episodes to changes in social zeitgebers due

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to travel across time zones (6), the birth of an infant (7, 8), death of a loved one (9), and employment and work-related changes (10, 11). Malkoff-Schwartz et al.'s (12) investigation of 39 bipolar disorder patients provided evidence that life events characterized by social rhythm disruptions were associated with the onsets of manic episodes. This finding was replicated in a later study, also conducted by Malkoff-Schwartz et al. (13).

Howland and Thase (14) suggested that individuals keeping regular daily schedules might be able to invoke artificial control over their biological rhythms. Given the power of social zeitgebers to entrain biological rhythms, social rhythm regularity may promote internal synchronization of circadian rhythms in individuals at risk for developing bipolar I and II disorders. The role of social rhythm regularity has been examined in association with affective symptomatology in patients with major depression (15, 16), the bereaved elderly (17), and rapid-cycling bipolar disorder patients (18). However, one limitation of the studies examining social rhythms is that participants are typically recruited from inpatient and outpatient treatment facilities and therefore may not be representative of all individuals with affective disorders. Depue et al. (19) advocated a high-risk paradigm because it yields a more representative sample of individuals at risk for bipolar disorder.

The aim of the present study was to further examine the role of social rhythms in bipolar spectrum individuals at risk for developing bipolar I disorder. First, we were interested in examining the relationship between social rhythms and participant diagnosis. We investigated the overall regularity of activities reported on an adapted Social Rhythm Metric (SRM) (20). We hypothesized that bipolar spectrum participants would report less regularity overall compared to normal controls. Second, consistent with the social zeitgeber theory of affective disorders, we hypothesized that participants, particularly bipolar spectrum individuals, reporting less social rhythm regularity would experience shorter time to onsets of affective episodes over a prospective follow-up period. This study is the first to examine lifestyle regularity in a sample at high risk for developing bipolar I disorder. In addition, it is the first to prospectively examine the relationship of regularity and the onset of affective episodes.

Method

Participant selection

The participants in this study were from the Wisconsin-Temple Longitudinal Investigation of Bipolar Spectrum Disorders (LIBS) Project, a prospective study investigating cognitive, psychosocial, and biological predictors of the course of bipolar spectrum disorders. Participants were undergraduates at Temple University, Philadelphia, PA and the University of Wisconsin, Madison, WI, USA. They were selected based on a two-phase screening process. In Phase I, the revised General Behavior Inventory (GBI) (19) was administered to approximately 20,500 students across the two sites. Students who met the initial GBI screening criteria (see Measures) were invited for Phase II: a semi-structured diagnostic interview using an expanded Schedule for Affective Disorders and Schizophrenia – Lifetime interview (exp-SADS-L) (21). Students meeting the *Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition* (DSM-IV) (22) and/or the Research Diagnostic Criteria (RDC) (23) criteria for bipolar II disorder (Bi II), cyclothymia (Cyc), or bipolar disorder not otherwise specified (BiNOS)[1] were invited to participate in the study. Bipolar spectrum participants were categorized and analyzed as Bi II or Cyc/BiNOS[2] participants.

Measures

Phase I: Self-report screening inventory. The revised GBI (19, 24) is a self-report questionnaire used in the LIBS project to identify potential bipolar disorder or normal participants to be invited for the Phase II diagnostic screening interview. The revised GBI is a time-efficient and economical screening measure to assess chronic affective disorders in large populations. It has good internal consistency (α = 0.90–0.96), test-retest reliability (r = 0.71–0.74), adequate sensitivity (0.78) and high specificity (0.99) for bipolar spectrum conditions (19, 24). In addition, this instrument has been extensively

[1]The bipolar NOS diagnosis included individuals who exhibited recurrent hypomanic episodes without diagnosable depressive episodes, individuals who exhibited a cyclothymic pattern but with hypomanic and depressive periods that did not meet minimum duration criteria for hypomanic and depressive episodes, and individuals with hypomanic and depressive periods that were too infrequent to qualify for a cyclothymia diagnosis. Participants who met criteria for bipolar I disorder were excluded because one of the aims of the LIBS Project was to predict conversion to bipolar I status over time.

[2]Cyclothymic and bipolar disorder NOS participants were combined together in a group distinct from bipolar II disorder participants because, unlike bipolar II individuals, neither group had a prior history of major depression.

validated in college, psychiatric outpatient, and offspring of bipolar I patient samples (19, 24). The revised GBI contains 73 items of three types: depression, hypomania/mania, and biphasic (24). Respondents receive two scores: a total on the depression (D) items and a total on the hypomania/mania and biphasic items combined (HB). We used the case-scoring method recommended by Depue et al. (24) to identify potential bipolar and normal participants. Only items rated a '3' (often) or '4' (very often or almost constantly) on the GBI 4-point frequency scale contributed a point toward the total score. Thus, GBI scores represent the number of symptomatic behaviors on which the respondent has met the criteria of duration, intensity, and frequency. Based on GBI D and HB scores, we identified two groups of potential participants using the following criteria: *Hi GBI Group* (potential bipolar spectrum): (i) a GBI-HB score ≥13 and (ii) a GBI-D score ≥11; and *Lo GBI Group* (potential normal controls): (i) a GBI-HB score < 13 and (ii) a GBI-D score < 11. These criteria were based on Depue et al.'s (19) findings and our pilot study in which Hi and Lo GBI students, using these cutoffs, were validated against diagnoses derived from SADS-L interviews.

Phase II: Diagnostic interview. The exp-SADS-L (21) is a semi-structured diagnostic interview that probes for the occurrence, duration, and severity of symptoms related to mood, psychotic, substance abuse and other disorders over the lifetime. Our exp-SADS-L was expanded in several ways: (i) probes were added to allow for the assignment of DSM-IV as well as RDC diagnoses; (ii) additional questions were added regarding depression, hypomania/mania, and cyclothymia to better capture the nuances of episodes and frequency and duration of symptoms; (iii) the order of interview questions was altered to increase the interview's efficiency; and (iv) sections were added to assess eating disorders, attention-deficit hyperactivity disorder (ADHD), and acute stress disorder, additional probes were added in the anxiety disorders section, and an organic rule-out module and medical history section were appended. The exp-SADS-L has yielded kappas ≥0.95 for major depressive diagnoses and ≥0.90 for all unipolar depressive diagnoses based on 80 jointly rated interviews (25, 26). An inter-rater reliability study based on 105 jointly rated SADS-L interviews for this project yielded kappas > 0.96 for bipolar disorder diagnoses. Extensively trained research assistants, blind to participants' Phase I group status and GBI scores, conducted the interviews. Consensus DSM-IV and RDC diagnoses were determined by a three-tiered standardized diagnostic review procedure involving senior diagnosticians and an expert psychiatric diagnostic consultant.

Social rhythm regularity measure. The SRM (20) was designed to quantify an individual's typical daily social rhythm patterns. The SRM is concerned with events and behaviors that occur on a regular daily basis. This self-report instrument captures the timing and frequency of specific activities and events whose regular occurrence contributes to the stability of an individual's daily routine. This measure was used to assess participants' social rhythm regularity and was administered at the beginning of the prospective follow-up period (Time 1). The SRM lists 17 daily activities, comprised of 15 specified and two individualized write-in items. The original instrument was found to be mildly consistent (i.e., $r = 0.44$, $p < 0.001$ between SRM scores in weeks 1 and 2) and valid (participants on vacation have considerably lower SRM scores) in a group of 50 healthy controls (15, 20). In addition, Monk et al. (15) found that the number of events reported per week did not differ significantly over a 12-week period for either patient or control groups.

Using a modified version of the SRM, participants were asked to endorse items if they had occurred regularly (i.e., a minimum of three times per week) and at approximately the same time (± 45 min) over the past month. Participants were asked to indicate the average frequency with which each endorsed item occurred per week (3–7 times). Two dependent measures were then derived for each participant: Regularity and Average Frequency. Regularity was defined as the number of activities endorsed as occurring three or more times within 45 min of the 'habitual' time during the week (possible range = 0–17 activities). Average Frequency was then calculated by averaging the frequencies of all items that had been endorsed as regular (possible range = 3–7 times). The modified SRM (M-SRM) was found to be consistent over time in a subsample of 101 bipolar spectrum participants and 100 normal controls in the LIBS Project from the first follow-up visit to the second and the second to the third (approximately eight months) ($r = 0.61$ and 0.62, respectively) (27). In addition, the Time 1 M-SRM predicted state SRM scores at the first follow-up (approximately four months later) with $r = 0.58$, establishing construct validity. Due to inconsistent reporting of write-in items across participants, only the 15 specified items were used for these analyses.

Prospective diagnostic measure. An expanded Schedule for Affective Disorders and Schizophre-

nia – Change interview (exp-SADS-C) (28) was used to assess the presence or absence of affective episodes at each four-month prospective assessment. The exp-SADS-C was expanded in the same manner as the exp-SADS-L and allowed the derivation of DSM-IV as well as RDC diagnoses. The exp-SADS-C probes for the occurrence, duration, and severity of symptoms related to mood, psychotic, substance abuse and other current disorders. Inter-rater reliability for the exp-SADS-C in joint ratings of 60 interviews in the LIBS Project was good (kappa > 0.80) (29). All interviewers, who had undergone extensive training for conducting semi-structured interview assessments, were blind to the participants' Phase I group status, SADS-L diagnosis, GBI scores, and SRM scores.

Procedures

Students who met the GBI cutoffs for Hi GBI and Lo GBI groups were invited to participate in Phase II of the screening process. Phase II consisted of completing the exp-SADS-L interview. Informed consent was obtained from participants who were told that the interview inquired about a broad range of problems and experiences that people sometimes have over their lifetime. All interviews were taped for the purposes of obtaining consensus diagnoses and inter-rater reliability checks. Students meeting DSM-IV and/or RDC criteria for Bi II, Cyc, or BiNOS but having no lifetime history of mania (or major depressive episodes if diagnosed with Cyc or BiNOS) were categorized as bipolar disorder participants. Normal controls were recruited and matched to bipolar disorder participants on demographics. Normal participants had no lifetime history of major depression, manic or hypomanic episodes, or of other Axis I psychopathology other than a possible specific phobia. Normal participants were excluded if they had any family history of mood disorders. Participants who met all of the above criteria were invited to participate in the LIBS project.

All participants in the final sample completed the M-SRM measurement as part of Time 1 of the LIBS project. Upon entering the longitudinal phase of the LIBS project, the exp-SADS-C was used to assess the presence or absence of affective episodes at each assessment. Participants were assessed for symptoms and the onset of full syndromal episodes of major depression, hypomania, and mania every four months. The present study was based on an average of 33.19 ± 16.89 months of follow-up. All participants were paid for their time.

Results

Participants

After the two-phase participant selection process (see Methods), the final bipolar disorder sample for the present study was composed of 57 Cyc/BiNOS participants (23 males, 34 females) and 149 Bi II participants (56 male, 93 females) aged 18–24 years (mean = 19.6 ± 1.6 years). The ethnic composition of the bipolar disorder sample was 68.9% Caucasian, 13.1% African American, 5.1% Hispanic, 3.6% Asian, 0.5% Native American and 8.2% Other. Of the 206 bipolar disorder participants, 31 (15.0%) had sought treatment (medication or psychotherapy) prior to the start of the LIBS Project and 63 (30.6%) sought treatment during the prospective follow-up phase of the study. Of these 63, 32 (15.5%) were treated with medications (with or without psychotherapy), 26 (12.6%) received psychotherapy only, and seven (3.4%) were hospitalized (including two who also received other treatment). The 32 participants who received medication were treated with mood stabilizers, primarily Depakote (10 participants), selective serotonin reuptake inhibitors or selective norepinephrine reuptake inhibitors (20 participants), and sleep medications (Ambien, 2 participants).

Normal controls were recruited and matched on a case-by-case basis to bipolar disorder participants on age, sex, and ethnicity. Normal participants had no lifetime history of major depression, manic or hypomanic episodes, or of other Axis I psychopathology, with the exception that they could have a specific phobia. They also had no family history of mood disorders. The final sample of controls included 86 males and 122 females aged 18–24 years (mean = 19.7 ± 1.5 years). Only participants with complete data available were included in the present study sample, resulting in the difference in sample size between bipolar disorder and normal participants. The ethnic composition of the normal sample was 72.8% Caucasian, 12.1% African American, 3.4% Hispanic, 4.4% Asian, 0.5% Native American and 6.8% Other.

Group differences on the study variables

Time in study. Given that follow-up time varied among participants, we conducted an analysis of variance to examine whether diagnosis was systematically related to length of time in the study (see Table 1). We found that the length of time in the study did not vary based on diagnosis, $F(2,411) = 1.01$, $p = 0.37$.

Table 1. Means and standard deviations (SD) of study variables by group

	Normal controls (n = 208)	Cyc/BiNOS (n = 57)	Bi II (n = 149)
Time in study	1013.26 (482.59)[a]	1050.95 (569.66)[a]	952.47 (512.63)[a]
Family history	0.00 (0.07)[a]	0.12 (0.33)[b]	0.14 (0.35)[b]
GBI – D	1.97 (2.34)[a]	22.15 (9.45)[b]	25.40 (8.86)[c]
GBI – HB	2.71 (3.07)[a]	16.15 (3.73)[b]	17.41 (3.82)[b]
Regular activities	9.62 (3.16)[a]	9.07 (3.02)[a]	8.47 (3.67)[b]
Frequent activities	5.23 (1.02)[a]	5.31 (1.13)[a]	5.32 (1.19)[a]
Major depressive Epi	0.11 (0.43)[a]	0.91 (2.12)[b]	1.86 (2.07)[c]
Hypo Epi	0.03 (0.24)[a]	6.81 (12.71)[b]	7.52 (9.96)[b]
Mania Epi	0.00 (0.00)[a]	0.26 (1.73)[b]	0.72 (3.03)[b]

[a,b,c]Within each row, means with a different superscript differ significantly (p = 0.05).
Cyc = cyclothymia; BiNOS = bipolar disorder not otherwise specified; Bi II = bipolar II disorder; GBI – D = General Behavior Inventory – Depression scale; GBI – HB = General Behavior Inventory – Hypomanic/Biphasic scale; Regular activities = number of regular activities of the 15; Frequent activities = frequency of regular activities of the 15; Epi = the number of prospective episodes experienced over the entire study duration; Hypo = hypomania.

Family history and initial symptom severity. Family history is an important risk factor in predicting bipolar disorder. We found that participants' family history of bipolar disorder varied by diagnosis, $F(2,383) = 13.92$, $p < 0.01$. Specifically, more participants in the Cyc/BiNOS and Bi II groups (14% and 16%, respectively) reported a family history of bipolar disorder than in the normal group (0%) (see Table 1). Table 1 also displays the initial GBI scores for the diagnostic groups. The groups differed significantly on initial GBI-D, $F(2,403) = 610.33$, $p < 0.001$, and HB, $F(2,403) = 884.54$, $p < 0.001$, scores. *Post hoc* comparisons with least significant differences (LSD) indicated that the Bi II group had higher initial depressive symptoms than the Cyc/BiNOS group ($p < 0.005$), which, in turn, had higher depressive symptoms than the normal group ($p < 0.001$). The Bi II and Cyc/BiNOS groups did not differ on initial hypomanic symptoms ($p < 0.06$) and both groups had higher hypomanic symptoms than the normal controls ($p < 0.001$).

Social rhythm regularity. Analysis of variance revealed that bipolar disorder participants reported significantly fewer regularly performed activities than normal participants, $F(2,411) = 5.18$, $p < 0.01$ (see Table 1). *Post hoc* analysis with LSD did not reveal significant differences between the Cyc/BiNOS and Bi II groups, $p = 0.25$. In addition, the frequency with which bipolar disorder and normal participants engaged in the activities that they endorsed as regular did not differ significantly, $F(2,406) = 0.27$, $p = 0.77$ (see Table 1).

Affective episodes. The normal and bipolar disorder participants differed in the number of affective episodes experienced over the study duration, $F(1,412) = 130.63$, $p < 0.01$. Specifically, the Cyc/BiNOS and the Bi II groups experienced more major depressive, hypomanic, and manic episodes over the study duration than the normal group (see Table 1). The Cyc/BiNOS and Bi II groups only differed in the number of major depressive episodes experienced, such that the Bi II group had more of these episodes (see Table 1). We also performed descriptive analyses to determine the proportion of participants experiencing affective episodes (see Table 2). The bipolar spectrum participants were more than eight times as likely to experience mood episodes during the follow-up period than the normal controls. Specifically, 9.1% of normal controls experienced an affective episode during the follow-up period compared to 75.4% of the Cyc/BiNOS group and 81.9% of the Bi II participants.

Table 2. Proportion of sample experiencing affective episodes during the follow-up period

Diagnostic group	Major depression	Hypomania	Mania	Any episode
Normal controls	7.7	1.9	0	9.1
Cyc/BiNOS	43.9	59.6	3.5	75.4
Bipolar II disorder	63.1	67.8	9.4	81.9

Values are reported as percent.
Cyc = cyclothymia; BiNOS = bipolar disorder not otherwise specified.

Second, we performed descriptive analyses to examine whether bipolar disorder participants' diagnoses changed, or worsened, throughout the course of the study. We found that 43.9% of the Cyc/BiNOS group experienced a major depressive episode during the longitudinal phase of our study. Thus, nearly half of the Cyc/BiNOS participants

experienced a worsening of their illness, as well as conversion to a Bi II disorder diagnosis. Similarly, 7.8% of the bipolar disorder participants (3.5% of the Cyc/BiNOS group and 9.4% of the Bi II group) experienced their first manic episode during the course of the follow-up period, representing a conversion to a Bi I diagnosis.

Survival analyses

Prior to carrying out the principal analyses of the study, distributions of predictor variables and covariates were examined for normality and multicollinearity, while Mahalanobis and Cook's distance statistics were used to identify potential outliers. These procedures failed to reveal any noteworthy departures from parametric assumptions.

Cox regression survival analyses were utilized to examine the relationship between social rhythm regularity, diagnostic group, and time (in days) to onset of participants' first prospective depressive and hypomanic or manic episodes. We utilized this analytic technique because it allows for varying lengths of follow-up in longitudinal studies and thus minimizes biases due to attrition (30). Further, survival analysis utilizes all available data at each time point and accounts for censored or missing data. We entered number of regular activities and diagnosis as the predictors and time to first affective episode (Model A) as the outcome variable (see Table 3). Utilizing the same predictors, we then entered time to the onset of specific types of affective episodes as the outcome variable; specifically, time to first major depressive episode (Model B) and time to first hypomanic or manic episode (these episodes were combined given the low incidence of mania in our sample) (Model C) (see Table 3). We coded diagnosis as '0' for normal controls, '1' for Cyc/BiNOS, and '2' for Bi II, so that we could compare the normal controls to both bipolar disorder groups individually (i.e., normal versus Cyc/BiNOS, normal versus Bi II). We did not obtain any significant Regularity X Diagnosis interaction effects. Therefore, these interactions were not entered in the three models.

Consistent with our hypothesis, regularity and diagnostic group both significantly predicted the time to participants' first affective episode (Model A). More specifically, we found that regularity and diagnostic group predicted the time to participants' first major depressive episode (Model B) and the time to participants' first hypomanic or manic episode (Model C) (see Table 3). For each model, less regularity predicted a shorter time to onset of each type of affective episode. It also interesting to note that diagnosis was a consistently stronger predictor of time to depressive and hypomanic or manic episodes than regularity (see Table 3).

Given that family history of bipolar disorder and initial symptom levels could influence time to episode onset, we reconducted the Cox regression survival analyses, including family history and GBI-D and HB scores as covariates. Diagnosis continued to significantly predict time to first

Table 3. Summary of Cox regression models predicting time to prospective affective episode

DV: Time to affective episode (n = 414)	β	*Wald*	Exp(β)
Model A: Predicting any affective episode			
Regularity	−0.06	8.88	0.94[c]
Diagnosis[a]			
Diagnosis (1)	2.71	96.84	14.99[d]
Diagnosis (2)	3.16	157.83	23.67[d]
Model A: With covariates			
Family history	0.27	1.17	1.31
GBI – D	0.00	0.03	1.00
GBI – HB	0.03	1.23	1.03
Regularity	−0.05	5.51	0.95[b]
Diagnosis[a]			
Diagnosis (1)	2.44	37.32	11.46[d]
Diagnosis (2)	2.81	51.35	16.57[d]
Model B: Predicting major depression			
Regularity	−0.06	5.03	0.95[b]
Diagnosis[a]			
Diagnosis (1)	1.77	30.61	5.86[d]
Diagnosis (2)	2.69	101.22	14.69[d]
Model B: With covariates			
Family history	−0.12	0.17	0.89
GBI – D	0.01	1.14	1.01
GBI – HB	0.02	0.92	1.03
Regularity	−0.05	3.57	0.95[e]
Diagnosis[a]			
Diagnosis (1)	1.15	6.14	3.16[c]
Diagnosis (2)	2.06	21.24	7.81[d]
Model C: Predicting hypomania and mania			
Regularity	−0.06	6.10	0.95[c]
Diagnosis[a]			
Diagnosis (1)	4.02	57.25	55.57[d]
Diagnosis (2)	4.51	76.28	90.88[d]
Model C: With covariates			
Family history	−0.38	1.91	0.68
GBI – D	−0.01	0.47	0.99
GBI – HB	0.03	1.58	1.03
Regularity	−0.05	4.39	0.95[b]
Diagnosis[a]			
Diagnosis (1)	3.82	38.56	45.85[d]
Diagnosis (2)	4.23	47.92	68.70[d]

[a]Normal control group was used as the reference group for diagnosis. Diagnosis (1) represents cyclothymia/bipolar disorder not otherwise specified group compared to normal control participants; Diagnosis (2) represents bipolar II disorder compared to normal controls.
[b]$p < 0.05$; [c]$p < 0.01$; [d]$p < 0.001$; [e]$p = 0.06$.
GBI – D = General Behavior Inventory – Depression scale; GBI – HB = General Behavior Inventory – Hypomanic/Biphasic scale.

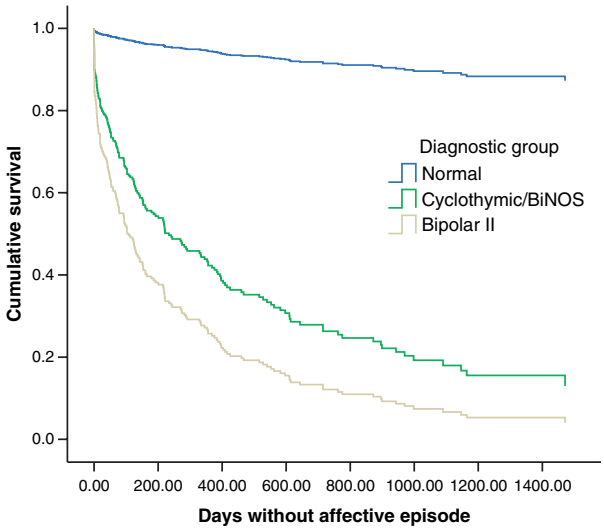

Fig. 1. Cox regression survival curve of time to first affective episode as a function of diagnostic status (n = 414). This graph illustrates that the cyclothymia/bipolar disorder not otherwise specified (BiNOS) group and the bipolar II disorder participants had a shorter length of time to their first affective episodes than the normal controls.

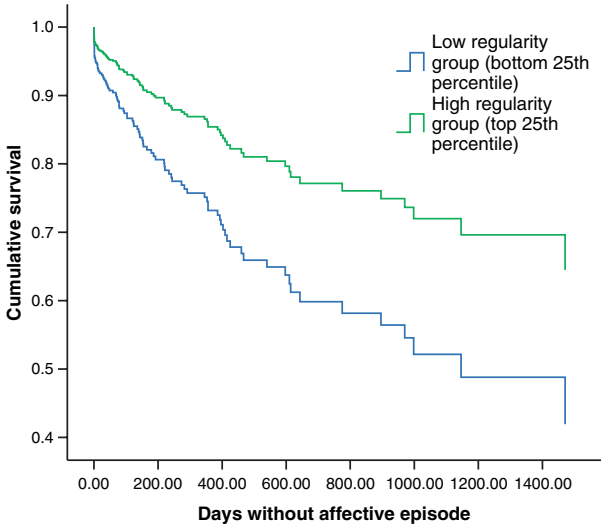

Fig. 2. Cox regression survival curve of time to first affective episode as a function of regulatory score (n = 218). This graph illustrates that the low-regularity group had a shorter length of time to their first affective episodes than the high-regularity group.

affective episode and to major depressive and hypomanic or manic episodes, controlling for family history and initial symptoms (see Table 3). Regularity continued to significantly predict time to first affective episode and to hypomanic or manic episodes, and to marginally ($p < 0.06$) predict time to first major depressive episodes (see Table 3), with family history and initial symptoms controlled. Family history and initial symptoms were not themselves significant predictors of time to the various affective episodes.

Fig. 1 illustrates the overall survival curve, or time to first affective episode, by diagnostic group. Fig. 2 shows the survival curve for participants as a function of their regularity score. Specifically, we graphed participants with low regularity scores [defined by a score in the lowest 25th percentile (range 0–7), n = 109] and participants with high regularity scores [defined by a score in the highest 25th percentile (range 12–15), n = 109] to highlight that individuals with lower regularity scores had a shorter length of time to their first affective episode than those with higher regularity scores.

Discussion

Our study utilized the M-SRM to examine the role of social rhythm regularity in predicting time to onset of affective episodes in a late adolescent/young adult sample with bipolar spectrum diagnoses at risk for developing more severe forms of bipolar disorder. The aims of this study were twofold. First, we were interested in investigating the relationship between the regularity of activities endorsed on the M-SRM and participant diagnosis. Our second aim was to examine the relationship between regularity, diagnosis, and the time to participants' first affective episodes during the prospective follow-up. Based on the social zeitgeber theory of affective episodes (5), we hypothesized that bipolar disorder participants would report less lifestyle regularity than the normal controls and that low social rhythm regularity would predict earlier onsets of their affective episodes.

As predicted, bipolar spectrum individuals reported significantly fewer regular daily activities than their matched normal control counterparts; however, the groups did not differ in the frequency with which they endorsed regular activities. Specifically, the Bi II group reported approximately one regular activity less than the control group; thus, they performed an activity at least three times less regularly per week over the study duration. A similar small, but significant, difference in regularity was found between individuals reporting bipolar disorder symptomatology and the control group (L. Sylvia, unpublished data). Thus, perhaps bipolar disorder individuals are particularly sensitive to small changes in their daily routine, or alternatively, normal controls may be better able to adapt to changes in their social rhythm regularity than the bipolar disorder group. This finding is also consistent with Ashman et al.'s (18) similar finding that rapid-cycling bipolar disorder patients

completed fewer activities on a regular basis than controls. Yet it is unclear whether decreased lifestyle regularity contributes to the development of bipolar disorder or is a consequence of bipolar disorder. Both hypotheses may, in fact, be true. Support for the former may be found in the relationship between social rhythm regularity and the prospective onset of affective episodes obtained in this study. These questions warrant further research in this area.

As hypothesized, less social rhythm regularity predicted a shorter time to onset of participants' first affective episode (and, thus, less time in a euthymic state) during the prospective follow-up. More specifically, regularity and diagnosis also significantly predicted the time to hypomanic and manic episode onsets during an average of 33 months following participants' initial reports of their social rhythm patterns. This finding is supported by previous studies that have found an increase in manic episodes after social rhythm disruptions in a bipolar I sample (12, 13); however, this is the first study to examine this relationship in a sample with bipolar spectrum disorders. Further, this is the first study to find a prospective association between social rhythm regularity and time to onset of participants' major depressive episodes. This novel finding suggests that individuals with unipolar depression may also be particularly susceptible to changes in their social rhythm regularity. Further, perhaps individuals with bipolar disorder are more vulnerable to social rhythm changes than individuals with unipolar depression, given that they experience both depressive and hypomanic or manic episodes.

These findings are congruent with Howland and Thase's (14) theory that individuals keeping regular sleep, meal and exercise schedules may be able to invoke artificial control over desynchronization of their biological rhythms. Further, recent evidence suggests that by increasing lifestyle regularity in bipolar disorder patients, one may be able to protect against future affective episodes (31). Our findings offer some support for the social zeitgeber theory and suggest that lifestyle regularity may be protective in delaying the occurrence of affective episode onsets (5). However, our findings do not distinguish the mechanism by which social rhythm irregularity may impact bipolar disorder episodes. For example, it has been suggested that bipolar disorder individuals have a trait-like abnormality in their circadian pacemakers that contribute to their social rhythm irregularity (32).

Alternative explanations for our results are possible. For example, a third factor may be responsible for both decreased social rhythm regularity and shorter survival times to affective episodes. For example, regularity may be a reflection of the severity of the disorder. Bipolar spectrum individuals who maintain more regular schedules may have less severe symptoms than those who maintain less regular schedules. Therefore, they may be less likely to experience affective episodes regardless of their daily routines. If this were the case, individuals diagnosed with Bi II disorder would be expected to differ significantly in regularity scores from cyclothymic and BiNOS participants. However, this was not found to be true. Moreover, decreased regularity predicted shorter time to affective episodes controlling for initial symptom severity. This suggests that regularity is not simply a reflection of the severity of bipolar spectrum disorders. An additional explanation, suggested by Wehr et al. (33), may be that sleep reduction impacts both regularity and affective episode onset. Although this is likely to have been captured in the regularity of wake and sleep times, it is possible that it was not.

Also of note, we found that bipolar spectrum participants experienced a worsening in the course of their illness over the study duration. These data support Akiskal and colleagues' (34, 35) proposal that individuals with cyclothymic symptomatology may be at risk for developing more severe forms of bipolar disorder. More specifically, nearly half of the cyclothymic individuals experienced a major depressive episode during the follow-up, converting their diagnosis to Bi II. Further, the onset of manic episodes for cyclothymic and Bi II participants represents a worsening of course and conversion to bipolar I disorder. The rate of conversion to bipolar I in our bipolar spectrum sample (7.8% over approximately a three-year period) falls within the range (5 – 15%) reported in the DSM-IV-TR (36) over a five-year period.

A possible explanation for these findings is that our sample may represent a largely untreated sample of bipolar disorder individuals; only 30.6% received treatment during the follow-up period. Research suggests that failure to receive appropriate treatment is not uncommon among bipolar disorder individuals. Bipolar patients involved in the Stanley Foundation Bipolar Treatment Outcome Network reported that the average length of time for first treatment was 10 years (37). As many as one- to two-thirds of individuals with bipolar disorder do not receive appropriate treatment due to misdiagnosis (38). In addition, a recent survey study found psychiatrists and primary care physicians failed to detect or misdiagnosed over half of the participants who screened positive for bipolar disorder (39). Thus, efforts need to be made to increase the awareness of the early signs and

symptoms associated with bipolar disorder, as well as treatment options for this disorder, to patients as well as mental health care providers. A second explanation of the worsening of course in this sample may be that irregularity of social rhythms may contribute to the onset of affective episodes in these vulnerable individuals.

Limitations of the current study also warrant further investigation. First, although the M-SRM measure was designed to capture trait regularity rather than state regularity, it was only completed (by all participants) once in the beginning of the longitudinal phase of the study. Individuals may vary in their stability of social rhythms across time. It is possible that the regularity reported on the adapted SRM may have changed over the course of the study. Readministering the measure at later points during the study would help to confirm that participants maintained their regularity patterns, particularly given that the M-SRM was only moderately consistent ($r = 0.61$–0.62) when administered four months apart in a subsample of our participants. Second, a criticism of self-report measures is that they are subject to reporting biases. It might be argued that the group differences in regularity may be the result of reporting bias rather than true differences in social rhythms. Perhaps bipolar disorder participants tend to report fewer activities as regular than normal participants. However, one would expect this bias to be reflected in the individualized write-in items. The number of regular write-in items reported by the two groups did not differ significantly. In addition, there were no group differences in the frequency of events reported as regular (occurring at least three times per week within ± 45 min). Therefore, it is likely that the differences reported by the groups were not the result of reporting biases.

Keeping in mind the limitations of this study, our findings suggest that exploring the impact of social rhythm regularity warrants further research. Specifically, lifestyle regularity may prove beneficial in preventing depressive and hypomanic or manic episodes in bipolar spectrum individuals. Interventions designed to regulate daily schedules may delay or prevent the onset of full syndromal affective episodes. Additional studies specifically designed to examine the longitudinal effects of interventions and treatments promoting lifestyle regularity in bipolar spectrum patients are recommended. Interpersonal and social rhythm therapy (IPSRT) was developed based on the circadian rhythm theory of bipolar disorder, recognizing the impact of social zeitgebers on these biological rhythms (40). IPSRT, which has been shown to result in more stable daily routines (41) and longer survival times between episodes (31) in bipolar disorder patients, may prove to be an effective means of supplementing current pharmacological treatments in managing affective episodes for patients with less severe bipolar spectrum disorders.

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