The Relationship Between Affective State and the Rhythmicity of Activity in Bipolar Disorder

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ABSTRACT

Objective: The aim of this study was to test the relationships between mood state and rhythm disturbances as measured via actigraphy in bipolar disorder by assessing the correlations between manic and depressive symptoms as measured via Young Mania Rating Scale (YMRS) and 30-item Inventory for Depressive Symptomatology, Clinician-Rated (IDS-C-30) scores and the actigraphic measurements of rhythm, the 24-hour autocorrelation coefficient and circadian quotient.

Method: The research was conducted at the University of Texas Southwestern Medical Center at Dallas from February 2, 2009, to March 30, 2010. 42 patients with a *DSM-IV-TR* diagnosis of bipolar I disorder were included in the study. YMRS and the IDS-C-30 were used to determine symptom severity. Subjects wore the actigraph continuously for 7 days. The 24-hour autocorrelation coefficient was used as an indicator of overall rhythmicity. The circadian quotient was used to characterize the strength of a circadian rhythm.

Results: A greater severity of manic symptoms correlated with a lower degree of rhythmicity and less robust rhythms of locomotor activity as indicated by lower 24-hour autocorrelation ($r = -0.3406$, $P = .03$) and circadian quotient ($r = -0.5485$, $P = .0002$) variables, respectively. No relationship was noted between the degree of depression and 24-hour autocorrelation scores ($r = -0.1190$, $P = .45$) or circadian quotient ($r = 0.0083$, $P = .96$). Correlation was noted between the 24-hour autocorrelation and circadian quotient scores ($r = 0.6347$, $P < .0001$).

Conclusions: These results support the notion that circadian rhythm disturbances are associated with bipolar disorder and that these disturbances may be associated with clinical signatures of the disorder. Further assessment of rhythm disturbances in bipolar disorder is warranted.

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Rhythm disruption is a hallmark of bipolar disorder.[1] Multiple models have been proposed to explain the disruptions in rhythms associated with bipolar disorder.[2–15] While no consensus has been reached on the direction of these disturbances, an integrating concept is that, rather than there being a stable change in the absolute timing of the circadian clock, there is an inherent instability in the circadian timing system and therefore an increased sensitivity toward temporal disorganization of physiologic rhythms in patients with affective disorders.[16] In support of this concept are several studies that report a wide variability in the phases of circadian rhythms in patients suffering from bipolar disorder.[12–15]

Actigraphy has previously been used to assess sleep, activity, and circadian variables in bipolar disorder.[5,17,18] Findings from these studies support the concept that there is a loss of rhythmicity in those suffering from the illness. Disturbances in the levels of locomotor activity are common in both manic and depressive phases of bipolar disorder.[17] Bipolar subjects show less locomotor activity when depressed and greater locomotor activity when manic.[5,17] Bipolar subjects have also demonstrated less stable circadian activity patterns, a greater fragmentation of activity, and a greater variability in 24-hour rhythm when compared to controls.[18]

Previous studies were designed to compare the differences in activity patterns and rhythms between bipolar patients and healthy controls or assessed activity levels in specific mood states. The aim of this study was to test the relationships between mood state and rhythm disturbances as measured via actigraphy in bipolar disorder by assessing the correlations between manic and depressive symptoms as measured via Young Mania Rating Scale (YMRS) and 30-item Inventory of Depressive Symptoms, Clinician-Rated scale (IDS-C-30) scores and the actigraphic measurements of rhythm the 24-hour autocorrelation coefficient and circadian quotient. We hypothesized an association between greater severity of affective symptoms and a decrease in the circadian rhythmicity of activity. We also hypothesized that mania would have a greater impact on rhythm disturbances than would depression.

METHOD

Subjects

Forty-two subjects diagnosed with bipolar I disorder were included in our evaluation. The research was conducted at the University of Texas Southwestern Medical Center at Dallas (UTSW) from February 2, 2009, to March 30, 2010. Subjects were recruited from various sources throughout Dallas County and represented a broad sampling of subjects diagnosed with the illness. Patients were recruited from county and community hospitals, the university medical center, community mental health clinics, and psychiatric and clinical research groups at UTSW. Subjects with a history of major neurologic impairment (ie, history of cerebrovascular accident), decompensated medical illness, mental retardation, traumatic brain injury, shift work or diurnal changes in work schedule 4 weeks prior to or during the course of the study, travel involving 3 or more time zones occurring 4 weeks prior to or during the course of the study, current use of hypnotic agents for sleep, and a recent history (1 month prior)

Clinical Points

- The findings of this study suggest that disturbances in biological rhythms may be associated with affective state, particularly mania, and may be correlated with other clinical signatures of bipolar disorder.
- Actigraphy presents a method to objectively and longitudinally assess chronobiology in bipolar patients.
- Actigraphic assessments may serve as potential objective measures of treatment response and may help to characterize sleep and rhythm disturbances associated with bipolar disorder.

of substance abuse or dependence were excluded from the study. The study was approved by the institutional review board of UTSW Medical Center and was consistent with standards for the ethical conduct of human research. All study participants provided written informed consent.

Clinical Assessments

DSM-IV-TR Axis I diagnosis of bipolar I disorder was confirmed by the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I/P).[19] All cases were then subject to a best-estimate diagnostic consensus including a minimum of 3 experienced clinicians in order to confirm the diagnosis of bipolar I disorder. Young Mania Rating Scale (YMRS)[20] was used to determine the degree of manic symptoms while the 30-item Inventory for Depressive Symptomatology, Clinician-Rated (IDS-C-30)[21] was used to determine the degree of depressive symptoms. Demographic and course of illness characteristics were collected on all participants.

Actigraphy

Actigraphy was used to collect data concerning locomotor activity.[22] For this study we utilized the Basic Motionlogger actigraph units (Ambulatory Monitoring, Inc; Ardsley, New York). Data were sampled in 60-second epochs. Subjects wore the apparatus continuously on the nondominant wrist for the duration of the study (7 days).

Statistical Analysis

Actigraphic data were analyzed by using Action 4 circadian rhythm analysis software (Ambulatory Monitoring, Inc; Ardsley, New York). The primary outcome of rhythmicity was the 24-hour autocorrelation coefficient[22] that represents the correlation of a time series with its own past and future values and may be taken as an indicator of the degree of rhythmicity. Higher 24-hour autocorrelation scores indicate a higher degree of rhythmicity. Lower scores indicate a lower degree of rhythmicity. Actigraph data were also analyzed via cosinor analysis.[6,23] The circadian quotient,[22] or amplitude-mesor ratio, was then calculated and used as a proxy for the robustness of rhythms. This measure provides an estimation of how well circumscribed periods of activity and sleep/rest are during the course of the day. Higher circadian quotient scores indicate a more robust rhythm. Lower scores indicate a less robust rhythm. The Pearson test was conducted to test the correlations between the degree of depressive and manic symptomatology, as defined by total scores on the IDS-C-30 and YMRS, respectively, and the actigraphic variables of interest (autocorrelation coefficient and circadian quotient). If positive correlations were noted, additional exploratory pairwise analyses via the Pearson test were conducted to test for correlations between autocorrelation coefficient and circadian quotient scores and individual items on clinical rating scales to explore the relationships between circadian rhythm variables and depressive and manic symptomatology. The Pearson test was also used to explore the correlation between the autocorrelation coefficient and circadian quotient scores to explore the relationships between the rhythmicity and rhythm robustness of physical activity. A significance value of .05 was set for all statistical tests.

Table 1. Sample Demographic, Clinical, and Course of Illness Characteristics

Demographic	Value
Bipolar I disorder, N	42
Age, mean (SD), y	41.0 (11.2)
Gender, n (%)	
Male	15 (36)
Female	27 (64)
Ethnicity, n (%)	
Caucasian	25 (60)
African American	14 (33)
Hispanic	3 (7)
Clinical characteristics	
YMRS score, mean (SD)	13.8 (8.0)
IDS-C-30 score, mean (SD)	20.7 (12.2)
Medicated, n (%)	33 (79)
Mood stabilizers	25 (60)
Atypical antipsychotics	18 (43)
Antidepressants	17 (40)
Unmedicated, n (%)	9 (21)
Course of illness characteristics	
History of hospitalization, n (%)	29 (69)
History of psychosis, n (%)	28 (67)
Age at onset of illness, mean (SD), y	17.5 (9.6)

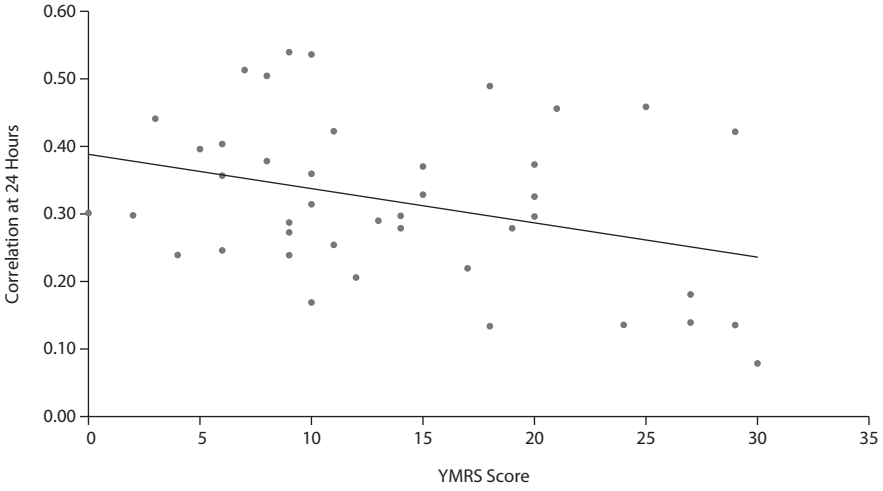
Abbreviations: IDS-C-30 = 30-item Inventory for Depressive Symptomatology, Clinician-Rated; YMRS = Young Mania Rating Scale.

RESULTS

Subject Demographic and Clinical Characteristics

Table 1 summarizes the demographic, clinical, and course-of-illness characteristics of the subjects included in the protocol. Twenty-one percent of subjects (n = 9) were medication free, while the remaining 79% of subjects (n = 33) were taking various medication combinations. Twenty-five subjects were taking mood stabilizers, 18 were taking atypical antipsychotics, and 17 were taking antidepressants. The mean (SD) YMRS score was 13.8 (8.0), while the mean (SD) IDS-C-30 score was 20.7 (12.2). No differences between medicated (21.4 [13.3]) and unmedicated (18.4 [6.9]) groups on IDS-C-30 scores were noted. Differences in YMRS scores ($P = .04$) were noted, with unmedicated patients (18.6 [7.2]) having a greater severity of manic symptoms when compared to medicated patients (12.5 [7.8]).

Figure 1. Correlation Between 24-Hour Autocorrelation Coefficient and YMRS Total Scores[a]



[a]An inverse correlation was noted between the circadian rhythm of locomotor activity and severity of manic symptoms as defined via autocorrelation coefficient and YMRS scores, respectively ($r = -0.3406$, $P = .03$).
Abbreviation: YMRS = Young Mania Rating Scale.

Table 2. Relationship Between YMRS Items, 24-Hour Correlation Coefficient, and Circadian Quotient

	Correlation With 24-Hour Autocorrelation Coefficient		Correlation With Circadian Quotient	
YMRS Item	*r*	*P*	*r*	*P*
1: Elevated mood	−0.1649	.2968	−0.1256	.4279
2: Increased motor activity and energy	−0.2037	.1956	−0.3737	.0148
3: Sexual interest	−0.1452	.3589	−0.2684	.0857
4: Sleep	−0.4698	.0017	−0.6798	<.0001
5: Irritability	−0.0024	.9882	−0.2165	.1686
6: Speech (rate and amount)	−0.2675	.0868	−0.3957	.0095
7: Language and thought disorder	−0.2654	.0894	−0.3047	.0497
8: Disturbances of thought content	−0.3116	.0446	−0.3649	.0175
9: Disruptive-aggressive behavior	0.1218	.4421	−0.1714	.2777
10: Appearance	−0.2311	.1409	−0.2125	.1766
11: Insight	−0.1273	.4218	−0.1251	.4299

Abbreviation: YMRS = Young Mania Rating Scale.

Relationships Between Actigraphic Measurements of Rhythmicity and Mood State Severity

The 24-hour autocorrelation scores were inversely correlated with YMRS scores ($r = -0.3406$, $P = .03$) (Figure 1). Pairwise correlations between 24-hour autocorrelation scores and YMRS items (Table 2) revealed that 24-hour correlation scores were correlated with decreased need for sleep (YMRS item 4) ($r = -0.4698$, $P = .002$) and disturbances of thought content (YMRS item 8) ($r = -0.3116$, $P = .04$). Trends toward inverse correlations between increased rate and amount of speech (YMRS item 6) and language and thought disorder (YMRS item 7) (both $P = .09$) and 24-hour autocorrelation scores were noted. No correlation between IDS-C-30 scores and 24-hour autocorrelation scores was noted ($r = -0.1190$, $P = .45$).

Circadian quotient scores were inversely correlated with YMRS scores ($r = -0.5485$, $P = .0002$) (Figure 2). Pairwise correlations between circadian quotient scores and YMRS items (Table 2) also indicated that circadian quotient scores were inversely correlated with increased motor activity and energy (YMRS item 2) ($r = -0.3737$, $P = .01$), decreased need for sleep (YMRS item 4) ($r = -0.6798$, $P < .0001$), increased rate and amount of speech (YMRS item 6) ($r = -0.3957$, $P = .01$), language and thought disorder (YMRS item 7) ($r = -0.3047$, $P = .05$), and disturbances of thought content (YMRS item 8) ($r = -0.3649$, $P = .02$). No association between IDS-C-30 scores and circadian quotient was noted ($r = 0.0083$, $P = .96$).

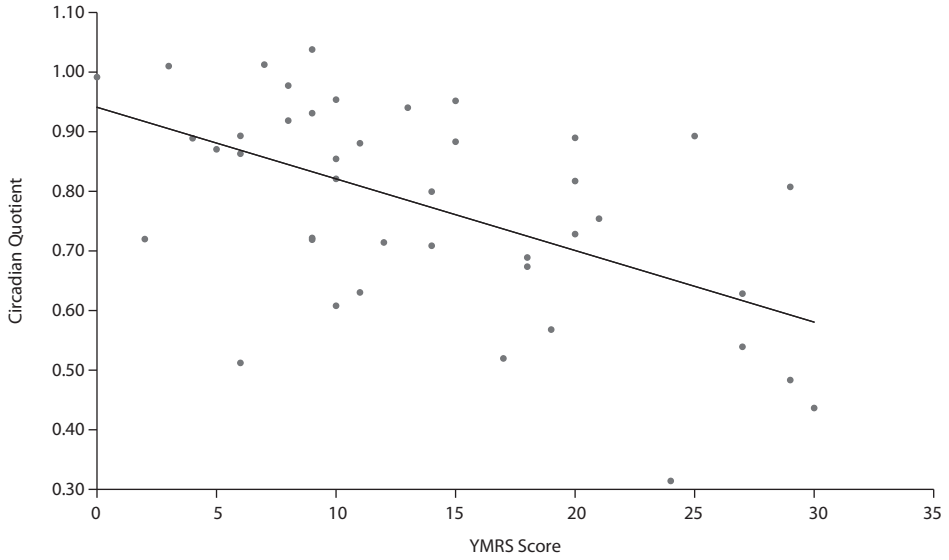
The relationships between severity of mood symptoms and the components used to calculate circadian quotients, amplitude and mesor, were explored. Amplitude did not correlate with either YMRS ($r = -0.0879$, $P = .5799$) or IDS-C-30 scores ($r = 0.2274$, $P = .1475$). Mesor did not correlate with either YMRS ($r = 0.1574$, $P = .3194$) or IDS-C-30 scores ($r = 0.1674$, $P = .2893$). Post hoc analysis also revealed a positive correlation between 24-hour autocorrelation and circadian quotient ($r = 0.6347$, $P < .0001$) (Figure 3).

In order to test the impact of medication status on actigraphic variables of rhythmicity, we compared the mean values between medicated and unmedicated patients. We found no statistical difference between these groups on either 24-hour autocorrelation ($P = .60$) or circadian quotient variables ($P = .11$).

DISCUSSION

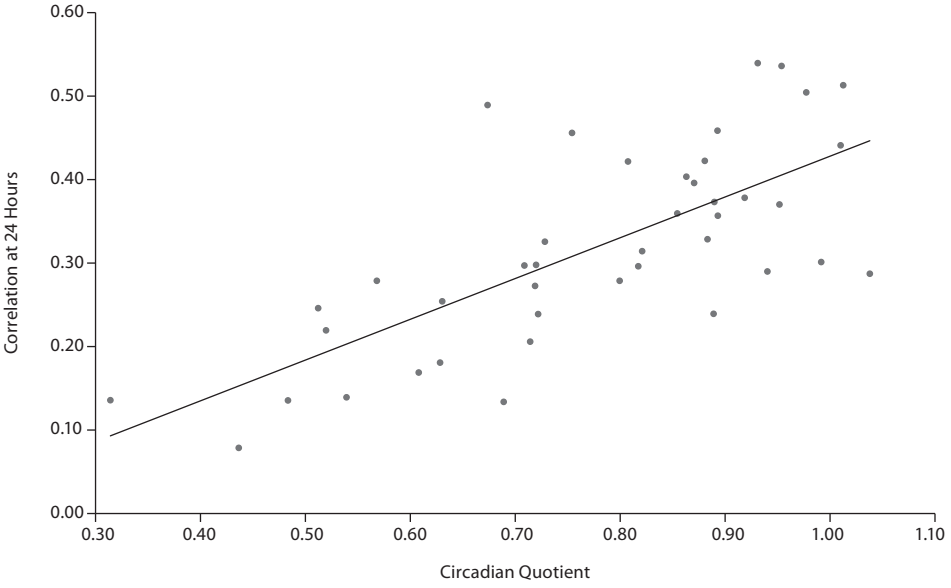
The findings of this study suggest a relationship between mood state symptom severity and rhythm disturbances of locomotor activity in subjects suffering from bipolar disorder. The results suggest that a greater severity of manic symptoms is related to a less robust circadian rhythm. Specifically, manic symptoms correlated with a lower degree of rhythmicity and less robust rhythms of locomotor activity, as indicated by lower 24-hour autocorrelation

Figure 2. Correlation Between Circadian Quotient and YMRS Total Scores[a]



[a]An inverse correlation was noted between the robustness of circadian rhythm of locomotor activity and severity of manic symptoms as defined via circadian quotient and YMRS scores, respectively ($r = -0.5485$, $P = .0002$).
Abbreviation: YMRS = Young Mania Rating Scale.

Figure 3. Correlation Between Circadian Quotient and 24-Hour Autocorrelation Scores[a]



[a]A positive correlation was noted between the robustness and rhythmicity of locomotor activity as defined via circadian quotient and 24-hour autocorrelation scores, respectively ($r = 0.6347$, $P < .0001$).

and circadian quotient variables, respectively. While the relationship noted between rhythm disturbances and manic but not depressive symptoms could potentially suggest a mood state phenomenon, these findings could also reflect a decreased acuity of actigraphy to characterize circadian rhythm disturbances.

Several relationships between rhythm disruptions and clinical characteristics of mania were observed. Clinical signatures that correlated with rhythm disturbances included decreased need for sleep, disturbances in content of thought and thought disorder, increase in rate and amount of speech, and increased motor activity and energy were noted. Of particular interest was the significant correlation between rhythm disturbances and a reported decreased need for sleep. These results are suggestive of a possible commonality or shared pathophysiology between sleep disruption and circadian rhythm disturbances and warrant further assessment.

Relationships between various markers of rhythmicity were also noted. A significant correlation between the 24-hour autocorrelation and circadian quotient scores suggests a relationship between the degree of circadian

rhythmicity and the robustness of circadian rhythms. Also, while a correlation between circadian quotient and YMRS scores was found, no correlation between the severity of manic symptoms and either amplitude or mesor was noted. This seems to suggest that the relationship between amplitude and mesor variables, rather than the variables individually, is correlated with symptoms of mania.

Limitations with the current analytic methods used to analyze actigraphic data should be mentioned. Many current analytic methods (ie, cosinor analysis) require that raw actigraphic data fit a specific mathematical model or set time frame (ie, 24 hours). Therefore, the use of more refined methods of actigraphy analysis that do not adhere to predetermined mathematical models or time constraints may better describe rhythm disturbances, especially in a population such as persons with bipolar disorder, in whom there is a great degree of disturbances in diurnal sleep-wake patterns. For example, the use of functional principal components analysis may allow for a more refined quantification of the actigraph data and the flexibility to search for functions representing activity patterns that may distinguish between subgroups and between-subject variability in bipolar patients.[24]

We did not find a statistically significant difference between medicated and unmedicated patients on either 24-hour autocorrelation or circadian quotient scores. It should also be noted that certain medications used to treat the illness may exert some of their therapeutic action via their influence on endogenous molecular clocks.[25–29] For example, both lithium[26,29,30] and valproic acid[26] have been shown to influence the rhythmic expression of circadian genes and the rhythmic properties of molecular clocks. While unmedicated patients had higher YMRS scores when compared to medicated patients, no difference in locomotor rhythms were observed between groups. These findings suggest that there may be other factors related to the manic state that more closely correlate with disturbances of rhythm.

The results of this study support the concept of a relationship between biological rhythm disruption and bipolar disorder, but caution should be taken regarding the inference of causality. While locomotor activity is influenced by the central circadian pacemaker, it is affected by many other variables and is not considered a robust marker of the central circadian clock. Future studies would benefit from the use of more refined chronobiological protocols to characterize and quantify rhythm disturbances and functioning of the central circadian clock in bipolar patients. Even with the limitations noted above, actigraphy does present a unique method to objectively and longitudinally assess chronobiological variables in bipolar patients.

Overall, our study supports the concept that there is significant mood instability associated with affective states in bipolar disorder. While we did not find a relationship between depression[12–15] and rhythm disturbances, we did find relationships between mania and rhythm disturbances.[12,13] As has been shown previously,[6,18] we have demonstrated the ability to measure rhythm disturbances utilizing actigraphy in patients with bipolar disorder. Ambulatory monitoring of activity patterns in conjunction with other chronobiological biomarkers may be valuable assessments that could potentially serve as physiological biomarkers of the illness and could lead to potential refinement of endophenotypes in bipolar disorder.

Drug names: lithium (Lithobid and others), valproic acid (Depakene and others).

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Potential conflicts of interest: **Dr Tamminga** serves as deputy editor for the American Psychiatric Association; is an ad hoc consultant for Astellas, Eli Lilly, Lundbeck, and PureTech Ventures; is a council member of the National Institute of Medicine; and is an advisory board member of Intra-cellular Therapies. She is also an unpaid council member of the Brain and Behavior Foundation, the Institute of Medicine, and NAMI; and is an unpaid volunteer and organizer for the International Congress on Schizophrenia Research. **Dr Tohen** has served as a consultant to Eli Lilly, GlaxoSmithKline, Wyeth, Roche, Merck, Lundbeck, and Otsuka. **Dr Suppes** has received funding or medications for clinical grants from the National Institute of Mental Health (NIMH), Sunovion, Elan Pharma, and the VA Cooperative Studies Program; has served on consulting/advisory boards of and has received travel expenses from Sunovion; and has received royalties from Jones and Bartlett. **Dr Gonzalez** reports no conflict of interest.

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