

## Biological rhythm disturbances in patients with bipolar disorder under remission

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### Abstract

**Background:** Biological rhythms are very important aspects governing the human life. The patients suffering from bipolar disorder have lot of issues which play an important role in the course of their illness. There is need to study their influence on the overall health in these patients especially who are under remission to prevent the relapse. This may help in improved compliance with better quality of living. Thus, reducing the need for hospitalizations.

**Methods:** 30 subjects with bipolar disorder according to ICD10 and fulfilling the criteria for remission were compared with 30 age matched normal subjects using the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) to assess biological rhythm disturbance. It is an 18-item interviewer-administered instrument which allows us to investigate the main areas related to circadian rhythm disturbance (sleep/social, activities, and eating pattern) in bipolar disorder.

**Results and discussion:** The BRIAN (total) scores were 23.37 +/- 2.76 for the patients vs. 18.43 +/- 0.77 for controls were significant. Significant correlation was observed between total duration of illness (in years) and total number of episodes in the sample patient population. The correlation was of statistical significance with relation to age of onset (in years) with BRIAN's Activity pattern ( $r=0.517$ ,  $p=0.003$  and Social pattern ( $r=0.409$ ,  $p=0.025$ ) and the BRIAN (Total) scores ( $r=0.486$ ,  $p=0.007$ ). The results suggest a potential association between biological rhythms and Bipolar disorder pathophysiology. There is need to for working other specific psychosocial interventions as a supplement to the psychopharmacological treatment of bipolar illness episodes.

**Keywords:** Bipolar disorder, Biological rhythms, Remission

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### Background

Bipolar disorder is major mental illness and a significant public health concern which has been understudied compared to other mental health disorders.<sup>(1)</sup> Research suggests that disruptions of internal biological rhythms may be responsible for the mood shifts experienced by bipolar disorder individuals.<sup>(2)</sup> According to the social zeitgeber theory of mood disorders, life events that disrupt social zeitgebers, defined as daily social rhythms or schedules are hypothesized to disturb circadian rhythms, which, in turn, precipitate bipolar symptoms and increase risk of relapses.<sup>(3,4)</sup> Therefore, treatments based on biological rhythm stability as well as control exposure to environmental stimuli may have therapeutic effects on illness episodes.<sup>(5)</sup> Delayed circadian phase of melatonin secretion has been reported in euthymic bipolar and depressive patients. Various phases of mood disorder are associated with circadian rhythm abnormalities. Sleep disturbances and instability of circadian rhythm continue when mood disorder patients are not acutely ill.

Howland and Thase<sup>(6)</sup> suggested that individuals keeping regular daily schedules might be able to invoke artificial control over their biological rhythms and may promote internal synchronization of circadian rhythms in individuals at risk. It has been hypothesized that abnormalities in the molecular clock underlie the development of mood disorders. Genes are considered to constitute an important etiologic factor in both mood

disorders and circadian rhythm. Circadian gene polymorphisms are associated with symptoms of mood disorder in preclinical and human studies.<sup>(7-10)</sup>

Malkoff-Schwartz et al.'s investigation of 39 bipolar disorder patients provided evidence that life events characterized by social rhythm disruptions were associated with the onsets of manic episodes.<sup>(11)</sup> Individuals at behavioral risk for bipolar disorder based on exhibiting hypomanic personality<sup>(12)</sup> or subsyndromal bipolar symptoms<sup>(13)</sup> exhibited lower social rhythm regularity. In euthymic individuals with bipolar II or cyclothymia diagnoses, low social rhythm regularity scores on a modified SRM at baseline predict a greater likelihood and shorter time to recurrence of both major depressive and hypomanic or manic episodes over prospective follow-up, controlling for baseline subsyndromal mood symptoms and family history of bipolar disorder.<sup>(14)</sup>

Despite all of the above, few studies have assessed biological rhythms in remitted bipolar patients.<sup>(15)</sup> In addition, most of them investigated sleep function exclusively, failing to take into account the other sensible areas involved in biological rhythms.<sup>(16,17)</sup> One such study is a compared bipolar I disorder patients ( $n=19$ ) with age- and gender-matched healthy controls, reporting that affected individuals presented higher sleep abnormalities in both objective and subjective measures than healthy control participants<sup>(18)</sup>. There is increasing evidence, however, that social rhythms, defined by attendance at work, engagement in social

activities or recreation, and exercise, may affect circadian regularity as a greater variability of social activities has been consistently related to sleep disturbance.<sup>(19,20)</sup>

The current study was carried out to assess biological rhythms in remitted bipolar patients and also to investigate possible correlations between biological rhythms, clinical course of illness, and residual mood symptoms in an Indian psychiatric hospital setting.

### Methods

**Subjects:** All patients (n=30) were enrolled from Tertiary Care Hospital. The inclusion criteria were (a) age >18 years, (b) fulfilling ICD-10(International Classification of Diseases-10) criteria for bipolar disorder, and (c) meeting remission criteria defined as a score  $\leq 8$  on the 17-item Hamilton Depression Rating Scale (HAM-D) and a score  $\leq 5$  on the Young Mania Rating Scale (YMRS) score for at least 2 months prior to the assessment of circadian rhythms. 30 Control participants matched by age, gender, and education with no psychiatric disorders that manifested interest in participating in the study were included. Both patients and controls were recruited from the hospital catchment area to ensure a similar socioeconomic pattern between groups.

**Instruments:** Biological rhythms interview of assessment in neuropsychiatry (BRIAN):

The Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) was used to assess biological rhythm disturbance. It is an 18-item interviewer-administered instrument which allows us to investigate the main areas related to circadian rhythm disturbance patterns (sleep/social, activities, and eating pattern) in bipolar disorder. In particular, the BRIAN assesses the frequency of problems related to the maintenance of circadian rhythm regularity.<sup>(21)</sup>

For instance, 'Do you have problems falling asleep at your usual time? How frequently?' (Items are rated using a 4- point scale: (1) = no at all, (2) = seldom, (3) = sometimes, and (4) = often). The total BRIAN scores range, hence, from 1 to 72, where the higher scores suggest severe circadian rhythm disturbance.

Manic and depressive symptoms were evaluated with the YMRS and the HAM-D, respectively. Clinical and demographic data were assessed using a standardized protocol. After receiving a complete verbal description of the study, informed consent was obtained from all participants.

**Statistical analysis:** Statistical analysis was performed using SPSS for Windows. Group comparisons (patients and controls) were made using Student's t test and  $\chi^2$  test when appropriated. Pearson's correlation coefficient was performed to examine the possible relationship between BRIAN scores, clinical variables, and functioning.

Demographic and clinical data have been represented in Table 1 and 2 respectively.

**Table 1: Demographic characteristics of the sample**

|                       | Patients<br>n=30<br>N (%) | Controls<br>n=30<br>N (%) |
|-----------------------|---------------------------|---------------------------|
| <b>Gender</b>         |                           |                           |
| Female                | 11(37)                    | 15(50)                    |
| Male                  | 19(63)                    | 15(50)                    |
| <b>Education</b>      |                           |                           |
| Literate              | 21(70)                    | 19(63)                    |
| Illiterate            | 9(30)                     | 11(37)                    |
| <b>Marital Status</b> |                           |                           |
| Married               | 20(67)                    | 18(60)                    |
| Unmarried             | 10(33)                    | 12(30)                    |
| <b>Family history</b> |                           |                           |
| Present               | 2(6.7)                    |                           |
| Absent                | 28(93.3)                  |                           |
| <b>Comorbidity</b>    | 7(23.3)                   |                           |

**Table 2: Clinical characteristics of the sample**

|                      | Patients |      | Controls |      |
|----------------------|----------|------|----------|------|
|                      | Mean     | SD   | Mean     | SD   |
| Age                  | 34.37    | 9.82 | 34.33    | 9.79 |
| Age of onset         | 25.17    | 7.56 |          |      |
| Number of Admissions | 1.9      | 1.49 |          |      |
| Total episodes       | 5.63     | 4.14 |          |      |
| Manic episodes       | 3.83     | 2.52 |          |      |
| Depressive episodes  | 1.83     | 2.48 |          |      |
| Suicidal attempts    | 0.5      | 1.14 |          |      |
| HAM-D                | 5.43     | 0.50 |          |      |
| YMRS                 | 3.97     | 0.18 |          |      |

SD=Standard Deviation

**Table 3: Table depicting student t-test across two groups**

|                 |          | N  | Mean  | T value | P value |
|-----------------|----------|----|-------|---------|---------|
| Brian (Sleep)   | Patients | 30 | 6.27  | 5.853   | 0.00    |
|                 | Controls | 30 | 5.10  |         |         |
| Brian(Activity) | Patients | 30 | 6.73  | 5.588   | 0.00    |
|                 | Controls | 30 | 5.13  |         |         |
| Brian(Social)   | Patients | 30 | 4.83  | 5.052   | 0.00    |
|                 | Controls | 30 | 4.07  |         |         |
| Brian(Diet)     | Patients | 30 | 5.53  | 7.425   | 0.00    |
|                 | Controls | 30 | 4.13  |         |         |
| Brian(Total)    | Patients | 30 | 23.37 | 9.426   | 0.00    |
|                 | Controls | 30 | 18.43 |         |         |

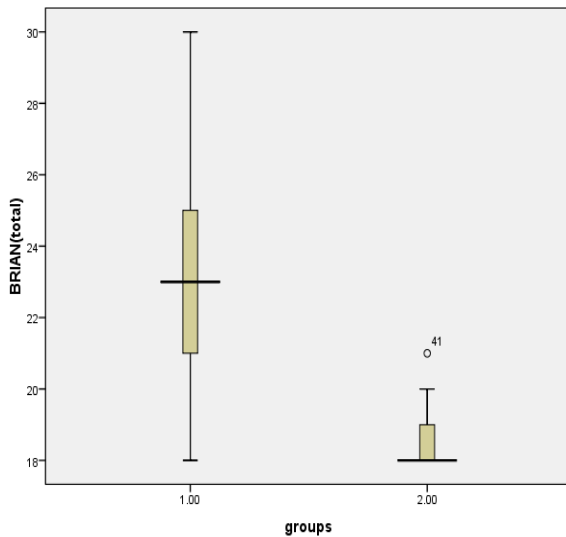
### Results

37% of the sample patient population was females. 70% of the patients' sample were literates and 20(67%) of the patient population were married. Majority 28(93.3%) of the patients did not have any

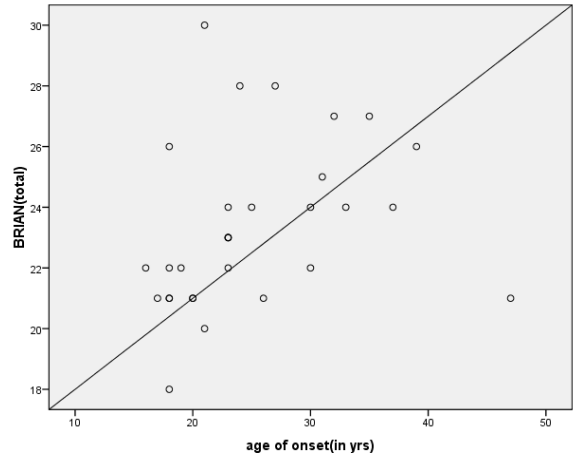
family history of the illness. The mean age (in years) of sample was 34.37 +/- 9.82 which was matched with control population (34.33 +/- 9.79). The total number of episodes were 5.63 +/- 4.14. The manic episodes were higher among the sample compared to the number of depressive episodes among the patients.

Bipolar patients experienced greater overall biological rhythm disturbance than the control group (BRIAN total scores 23.37 +/- 2.76 for the patients' vs. 18.43 +/- 0.77 for controls). There was statistical significance for the results. Significant correlation was observed between total duration of illness (in years) and total number of episodes among the patients in the sample population. As the duration of the illness increased, there was an increase in the number of episodes. The correlation was significant among age of onset (in years) with BRIAN {(Activity) (r=0.517, p=0.003). A positive correlation was observed with age of onset (in years) and BRIAN(Social) (r=0.409, p=0.025)} and also with the BRIAN (Total) scores (r=0.486, p=0.007).

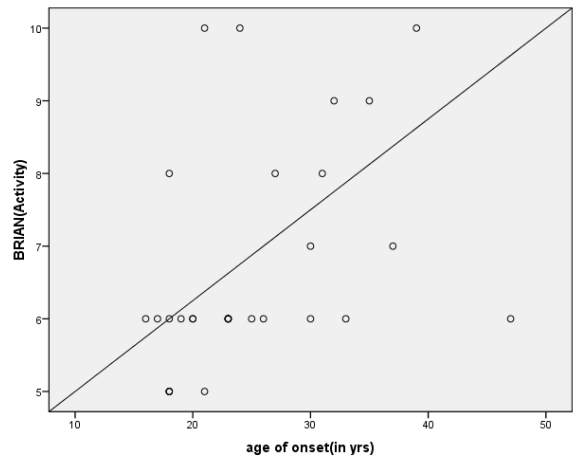
Table 3 depicts a significant score for t-test BRIAN (total) (t=9.426). The individual patterns of BRIAN i.e. Sleep, Activity, Social and Diet, had statistical significance. The scores were more in the patients compared to the controls. The results are under normal values but showed significant results.



**Fig. 1: Graph comparing the BRIAN(total) scores of patients vs controls**



**Fig. 2**



**Fig. 3**

**Discussion**

The results suggest a potential link between biological rhythms and Bipolar disorder pathophysiology as seen in the previous studies.<sup>(2)</sup> Lesser sleep duration was associated with elevation of mania while sleep variability was associated with both mania and depression.<sup>(4)</sup> There are significant differences between groups in social and activity patterns similar to previous studies.<sup>(22)</sup> Biological rhythm abnormalities have also been reported in unipolar depression,<sup>(14)</sup> in high risk subject of bipolar spectrum disorders,<sup>(23)</sup> in rapid cycling bipolar patients.<sup>(24)</sup> Social rhythm disturbance caused worsening of long-term outcome<sup>(14)</sup> of the affective episodes. Significant differences were observed between individuals at high risk of bipolar spectrum disorders with regard to the activity patterns and sleep parameters such as duration, fragmentation, and efficiency.<sup>(23)</sup> There is need to for working other specific psychosocial interventions as a supplement to the psychopharmacological treatment of bipolar illness episodes like interpersonal social rhythm therapy.

## Limitations

Our results should be interpreted carefully for several reasons. The sample of 30 patients and 30 controls is a small sample which needs to be evaluated more to get better results. It is part of bigger sample we would like to work on to get better results and more evidence to work other supplementary interventions. Many of the patients had previously received counseling which may have increased their daily activity regularity. Although the BRIAN is an interviewer-administered instrument, it is also based on patients' self-report, which may have influenced the results. Further studies have to be in order to investigate the possible correlations between subjective (BRIAN) and objective measures (e.g. Polysomnography). This is a cross-sectional study which does not allow us to determine the direction of the relationship between circadian abnormalities and mood symptoms. Longitudinal studies are needed to clarify this issue. The use of more objective assessment tools should be considered.

## Conclusion

This study showed that biological rhythm disturbances are common in bipolar patients suggesting an important link between rhythm instability and bipolar disorders. Specific psychosocial interventions need to be applied as part of a supplementary therapy for maintenance of the treatment in bipolar disorder to improve the quality of living and reduce the need for hospitalizations.

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