Journal of Affective Disorders 186 (2015) 145–148

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Short Communication

Biological rhythms in bipolar and depressive disorders: A community study with drug-naïve young adults

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ARTICLE INFO

Article history:
Received 29 April 2015
Received in revised form
19 June 2015
Accepted 4 July 2015
Available online 21 July 2015

Keywords:
Mood disorders
Bipolar disorder
Biological rhythm
Major depressive disorder
Community sample
Young adults.

ABSTRACT

Aim: To assess biological rhythm disruptions among drug-naïve young adults with bipolar disorder (BD), major depressive disorder (MDD), and community controls.
Methods: This was a cross-sectional study nested in a population-based study. BD and MDD were diagnosed using the Structured Clinical Interview for DSM-IV. Biological rhythm disruptions were assessed using the Biological Rhythm Interview of Assessment in Neuropsychiatry (BRIAN).
Results: Two hundred seventeen subjects were assessed (49 BD, 74 MDD, and 94 community controls). Biological rhythm disruption was higher in subjects with BD (40.32 ± 9.92; $p < 0.001$) and MDD (36.23 ± 8.71; $p < 0.001$) than community controls (27.67 ± 6.88). Subjects with BD had a higher BRIAN total score ($p = 0.028$) and higher disruption in sleep/social domains ($p = 0.018$) as compared to MDD. In addition, the BRIAN scores were higher in current MDD, euthymic BD, and BD in current episode group, as compared to community controls.
Limitation: Cross-sectional design. Absence of assessment of biomarkers of biological rhythms.
Conclusion: Bipolar disorder and major depressive disorder are associated with disruption in biological rhythm. In addition, disruption in sleep/social rhythms is higher in subjects with BD when compared to subjects with MDD. We also verified biological rhythm disruption in subjects with BD during euthymic status, but not in remitted MDD. Regulation of biological rhythm may be a means to identify patients with mood disorders and potentially differentiate MDD from BD.

1. Introduction

Biological rhythm is a concept that comprehends cyclical variations of both physiological and behavioral functions (Soria and Urretavizcaya, 2009). Dysregulation of internal and neurobiological rhythms reflects changing patterns of serotonin, norepinephrine and dopamine secretion (Salgado-Delgado et al., 2011). Disruption of internal time can lead to further induction of mood and sleep-wake cycle changes (Robillard et al., 2013).

In subjects with bipolar disorder (BD), abnormalities in activities, social, sleep, and eating rhythm patterns can persist even during remission, as subsyndromal symptoms (Kapczinski et al., 2009). Changes in biological rhythm may be caused by sleep disturbances (Harvey et al., 2009), routine alteration (Gindre and Swendsen, 2010), absence of external time regulators ("*zeitgebers*") (Haus and Smolensky, 2006), and stressful life events (Malkoff-Schwartz et al., 2000). These disruptions are important correlates of acute manic episodes onset (Harvey, 2008), and may represent vulnerability markers of hypomanic episodes (Ankers and Jones, 2009). Previous studies suggest that disruption in biological rhythms may also be linked to the development, progression, or relapse of mood disorders, such as major depressive disorder (MDD) and seasonal affective disorder (McClung, 2007; Salgado-Delgado et al., 2011).

Current studies with clinical samples have already provided data supporting disruption of biological rhythms in subjects with mood disorders, particularly those with BD and multiple episodes (Giglio et al., 2010). The advantage of studying samples in early adulthood is that they are still unencumbered by cumulative

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http://dx.doi.org/10.1016/j.jad.2015.07.004
0165-0327/

effects of multiple, hospitalizations and polypharmacy. In addition, these subjects are usually in the initial stages of the disease, and less affected by neuroprogression. What is not known is if disruption in biological rhythms occurs in non-clinical samples. The aim of the present study is to assess the biological rhythms in a community sample of drug-naive young adults with bipolar disorder, major depressive disorder, and matched community controls.

2. Methods

This was a cross-sectional assessment nested in a population-based study with drug-naive young adults aged 18–24 years. Full details on the larger study have been published elsewhere (Jansen et al., 2011). Briefly, the sample consisted of 1560 participants from 18–24 years-old living in urban area of the city of Pelotas, southern Brazil. Sample selection was performed by clusters, in the period ranging from August 2007 to December 2008, in a population of 39,667 people in the targeted age range in the Brazilian census of Pelotas 448 sectors (IBGE, 2008). In order to ensure the necessary sample inclusion, 89 census-based sectors were systematically drawn. After the subjects were identified, study subjects were invited to participate, signed an informed consent, answered questionnaires and structured diagnostic interviews. The project was approved by the Ethic Committee at the Catholic University of Pelotas (UCPel).

In an initial psychopathology screening, the whole population underwent the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). For the purposes of the current study, we attempted to recruit young adults with past or current history of manic episodes. We were able to detect 93 subjects with BD. Additionally, 93 subjects with major depressive disorder without history of manic/hypomanic episodes, and 93 young adults without any history of affective disorder were randomly selected in the community and matched according to sex, age, and socioeconomic situation. Importantly, we did not exclude people on account of any other mental disorders. For statistical analyzes, we excluded medicated subjects. In order to improve diagnostic reliability, we used the Structured Clinical Interview for DSM-IV (SCID) (Del-Ben et al., 1996). The interviews were conducted by two Ph.D. students, who underwent extensive training under the supervision of a senior researcher.

Biological rhythms were assessed using the *Biological Rhythm Interview of Assessment in Neuropsychiatry* (BRIAN). This scale includes 18 items divided in three domains: activity, sleep/social rhythm, and eating pattern. The validity and reliability studies of the Portuguese BRIAN version include information about its factor analysis (Giglio et al., 2009). The severity of depressive symptoms was assessed using the *Hamilton Depression Rating Scale* (HDRS) (Hamilton, 1967), and the severity of manic symptoms was assessed using the *Young Mania Rating Scale* (YMRS) (Vilela et al., 2005).

Descriptive analyses are presented in percentage, means and standard deviation, or median and interquartile range. Demographic and clinical characteristics were analyzed using chi-square, ANOVA, and Kruskall–Wallis tests, as indicated in the table. BRIAN scores presented a normal distribution and were tested by parametric ANOVA test with Bonferroni correction for multiple comparisons. In addition, we performed a multivariate model analysis using linear regression to test the difference on the BRIAN scores across diagnostic groups, adjusting for demographic and clinical variables. Multiple linear regression was also run to investigate the association between biological rhythm and current mood state: remitted MDD, current MDD, euthymic BD and BD in current episode. The assumptions of linearity, independence of errors, homoscedasticity, unusual points and normality of residuals were met. Sex was associated with mood disorder and was considered a confounding variable.

3. Results

Two-hundred thirty one drug-naïve young adults composed our final sample (83% of the originally intended sample). We excluded 14 medicated subjects (8 MDD and 6 BD). Two hundred seventeen drug-naïve young adults were included in the analyses. Forty-nine fulfilled criteria for bipolar disorder, 74 for major depressive disorder, and 94 subjects were included as community controls. The sample characteristics are showed in table 1.

Disruption in biological rhythm was higher in subjects with BD (40.32 ± 9.92) and MDD (36.23 ± 8.71), as compared to community controls (27.67 ± 6.88). The differences in BRIAN scores between groups were observed even when adjusted for sex and severity of depressive symptoms in the regression analysis (*B coefficient* 3.06; 95% CI 1.38–4.75; $p < 0.001$). Moreover, biological rhythm disruption was higher in subjects with BD, as compared to subjects with MDD (p 0.017). This difference was also observed after adjusting the analyses for severity of depressive symptoms (*B coefficient* 3.06; 95% CI 1.38–4.75; p 0.024). In addition, subjects with BD presented higher BRIAN total score (p 0.028) and higher disruption in sleep/social domain (p 0.018), as compared to MDD (Fig. 1).

Fig. 2 shows differences in BRIAN scores across mood states according to Bonferroni post-hoc test. We verified higher disruption in biological rhythms of subjects with current MDD ($p < 0.001$), and in subjects with BD in euthymic (p 0.011) and depressive states ($p < 0.001$), as compared to community controls. In addition, subjects in remitted MDD showed higher biological rhythm disruption when compared to subjects with BD in current episode (p 0.010). There were no statistically significant differences in the other comparisons between groups.

Biological rhythm was associated with bipolar disorder independently of current mood state (r^2 0.31; $p < 0.001$). This was observed in Euthymic BD (*B coefficient* 8.86; 95% CI 3.46-14.26); and BD in current episode (*B coefficient* 12.38; 95% CI 10.22–16.54). In subjects with MDD, the biological rhythm disruption was

Table 1
Sample characteristics among groups.

Characteristic	BD	MDD	Community control	*p* value
	$n=49$	$n=74$	$n=94$	
Age**	21.88 ± 2.31	21.86 ± 2.04	22.40 ± 2.25	0.208
Female sex*	37 (75.5%)	56 (75.7%)	54 (57.4%)	0.018
Years of education**	8.95 ± 3.58	8.91 ± 2.67	9.70 ± 3.17	0.242
Current state*				< 0.001
Euthymic	11 (22.4%)	16 (21.6%)	–	
Depressive episode	28 (57.1%)	58 (78.4%)	–	
Mania/mixed episode	10 (20.4%)	–	–	
HDRS score***	13 (7.50–21.00)	13 (7.00–18.00)	–	< 0.001
YMRS score***	1 (0-8.75)	–	–	< 0.001
BRIAN score**	40.32 ± 9.92	36.23 ± 8.71	27.67 ± 6.88	< 0.001

BD = bipolar disorder; MDD = major depressive disorder; HDRS = hamilton depression rating scale; YMRS = young mania rating scale; BRIAN = biological rhythm interview of assessment in neuropsychiatry.

* Percentile, Chi-square test.
** Mean and standard deviation, One-way ANOVA test.
*** Median and interquartile range, Kruskall-Wallis test.