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Chronobiological dis-rhythmicity is related to emotion dysregulation and suicidality in depressive bipolar II disorder with mixed features

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ABSTRACT

In Bipolar Disorder, chronobiological rhythm alterations play a key role by negatively influencing its entire trajectory. Our aim was to assess their potential association with emotion dysregulation and suicidality in subjects with Bipolar Disorder. Eighty-five patients with Bipolar Disorder - II depressive episode with mixed features were recruited and 35 as healthy controls. Subjects were evaluated with SCID-DSM-5, the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN), the DERS: Difficulties in Emotion Regulation Scale, the Beck Depression Inventory-II (BDI-II), the Young Mania Rating Scale (YMRS) and the Scale for Suicide Ideation (SSI). When compared to healthy controls, subjects with bipolar disorder showed significantly higher scores in the BRIAN, the DERS, the BDI-II, the YMRS and the SSI total scores. Chronobiological dis-rhythmicity was significantly related to the severity of depressive symptoms, emotion dysregulation, and suicidality in bipolar individuals. In particular, the dis-rythmicity of the sleep/wake pattern showed a significant correlation with manic symptoms, the dis-rythmicity of daily activities with depressive symptoms and emotion dysregulation and that of social life with suicidality. Emotion dysregulation played as a mediator for the association between chronobiological dis-rhythmicity and depressive symptoms (mediated effect = 3.25, $p = 0.001$) and for social life dis-rhythmicity and suicidality (mediated effect = 2.52, $p = 0.011$) as well. Therefore, our findings showed that chronobiological dis-rhythmicity in bipolar individuals was related to the severity of mood swings, emotion dysregulation and suicidality. The assessment of potential alteration in chronobiological rhythms should be investigated in the clinical setting in subjects with bipolar disorder to identify those who may benefit from early chronobiological intervention.

Introduction

Mood disorders, include a spectrum of conditions encompassing from elevated mood such as mania/hypomania to depressed mood (APA, 2013); major forms, such as major depressive unipolar and bipolar disorders, are amongst the most prevalent and the most likely to be recurrent, chronic and disabling (Kupfer et al., 2012; Wittchen, 2012; APA, 2013; Schaffer et al., 2015). Therefore the impact on public health represents a major concern leading to global burdens of disease in terms of disability, morbidity, premature mortality (Wittchen, 2012; Whiteford et al., 2013; Ferrari et al., 2014) and to a significant risk for suicidality (Isometsä, 2014; Schaffer et al., 2015). The understanding of the mechanism involved in the development and maintenance of bipolar disorders should thus be considered as a priority to identify potential early markers that could help in informing preventive strategies and/or improving treatment strategies.

Compelling evidence has suggested that mood disorders are frequently associated with a malfunction of the circadian system that may play a pathogenetic role (for an overview see Harvey, 2011; McClung, 2013). According to the "circadian hypothesis of mood disorders" the de-synchronization of the master biological clock of the hypothalamus, the suprachiasmatic nuclei, constitutes a hallmark of mood disorders contributing to their maintenance (Harvey, 2011; McClung, 2013; Dellaspezia and Benedetti, 2015). It has been shown that the majority of individuals with bipolar disorder presents alterations in the circadian rhythmicity, with abnormalities in physiological and behavioral time-keeping processes across the 24-h including social life, activities, eating and sleep/wake patterns, prior and during the depressive or manic episodes and euthymia as well (Harvey, 2008; Giglio et al., 2010; Harvey, 2011; Dellaspezia and Benedetti, 2015; Abreu and Bragança, 2015; Alloy et al., 2017). In particular, chronotypes represent the natural circadian individual propensity for sleep timing and daily activities

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performing, and among all, eveningness, characterized by the later bed and rising times, more irregular sleep–wake up habits and ascending evening energy (Adan et al., 2012), is the most frequent in subjects with bipolar disorder (Giglio et al., 2010; Harvey, 2011; Cretu et al., 2016). Eveningness is considered a precursor of bipolar disorder and a factor that may contribute to bipolar disorder relapse and recurrence (Giglio et al., 2010; Harvey, 2011; Cretu et al., 2016). Similarly, among the other patterns of circadian sleep dis-rhytmicity, irregular and delayed sleep patterns are frequent across mood episodes and inter-episode periods of bipolar disorder (Kanady et al., 2015): all these circadian abnormalities have been considered biomarkers of bipolar disorder (for an overview see Milhiet et al., 2014).

Although biological rhythm dysregulation being suggested as a potential early marker and associated with poor functioning in bipolar disorder (Harvey, 2008; Dellaspezia and Bendetti, 2015; Pinho et al., 2016), the association with mood/emotion dysregulation and suicidality is to date poorly understood.

Particularly, emotion dysregulation has been proposed as a critical component in the development and maintenance of mood disorders with a feedback recursively and dynamic loop reinforcing mood dysregulation (Gross and Thompson 2011; Hofmann et al., 2012; Herny et al., 2012). Emotion dysregulation occurs when the modulation of some features of emotional functioning is problematic in terms of early emotional processes, the appraisal and evaluation of stimuli and emotional response with its behavioral and physiological components in both the immediate context and in the long-term objectives/goals of individuals (Gross and Thompson 2011; Hofmann et al., 2012). In particular, emotional hyper-reactivity has been related to mood instability, impaired decision making, aggressive and impulsive behaviors, increased risk of substance abuse and suicidality in individuals with bipolar disorder (Gross and Thompson 2011; Hofmann et al., 2012). Several neurobiological studies which have focused on the link between emotional dysregulation and mood disorders have shown a dysfunction in the brain serotonergic and dopaminergic systems in both the pathophysiological mechanisms of mood disorders and in emotion dysregulation (Wessa and Linke, 2009; Hofmann et al., 2012). Particularly, a dysfunction in the amygdala-frontal circuit has been related to emotion dysregulation observed in mood disorders due to a compromised connectivity between the pre-frontal cortex and limbic regions with the top-down impaired regulation of emotions (Wessa and Linke, 2009).

Although emotional dysregulation has been linked to mood instability, aggressive and impulsive behaviors, increased risk of suicidality in individuals with bipolar disorder (Gross and Thompson 2011; Hofmann et al., 2012; Herny et al., 2012) its association with the circadian dis-rhythmicity in bipolar disorder remains unclear.

Since circadian rhythm alterations seem to play a key role in bipolar disorder our study was aimed to investigate their potential association with manic/depressive symptoms, emotion dysregulation and suicidality in individuals with bipolar disorder. We assessed circadian rhythms with The Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) (Giglio et al., 2009) . We also explored the potential processes underling the relationship between these variables by conducting mediation analyses.

2. Methods

2.1. Selection of subjects and psychometric questionnaires

The current study included a subsample of participants from the ongoing main research plan aimed to evaluate circadian dysregulation in different types of mood disorders. This study included subjects with diagnosis of Bipolar Disorder type II depressive episode with mixed features according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (APA, 2013) who were hospitalized at the Psychiatry Unit of the University of Pisa, Italy, from December 2015 to April 2017. Subsequently when the study will be completed the role circadian dysregulation in other forms of mood disorders will be evaluated and compared.

A group of healthy subjects who were matched for gender and age were recruited from among university personnel.

Subjects were included if they were aged between 18 and 65 years and expressed the willingness to sign an informed consent to the study. All subjects were evaluated with a set of questionnaires that included the structured interview for DSM-5 (Structured Clinical Interview for Axis I Disorders- SCID-I) (First et al., 2017) to assess the presence of current or lifetime psychiatric diagnosis, the Italian version of the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) (Giglio et al., 2009; Moro et al., 2014) to evaluate circadian rhythms, the Difficulties in Emotion Regulation Scale (DERS) (Gratz and Roemer, 2004; Sighinolfi et al., 2010) to evaluate emotion dysregulation, and the Scale for Sucide Ideation (SSI) to evaluate suicidality (Beck et al., 1979). The Beck Depression Inventory- II (BDI-II) (Beck et al., 1996) and the Young Mania Rating Scale (YMRS) (Young et al., 1978) were used to evaluate respectively depressive and manic symptoms. At the baseline all the subjects also completed clinical report forms which included current pharmacological therapy.

The exclusion criteria for subjects with Bipolar Disorder were: current and lifetime diagnosis of substance abuse, depressive episode with psychotic features, other types of bipolar disorder, cognitive impairment (Mini Mental State Evaluation for the Italian version Measso et al., 1993).

Healthy controls were recruited from among university personnel. Participants underwent to a face-to-face assessment and completed the same set of questionnaires used for the subjects Bipolar Disorder. The exclusion criteria for healthy controls were the following: i) past or current diagnosis of mental diseases; ii) the BDI-II score ≥ 13; iii) the YMRS score ≥ 7; iv) the SSI score ≥ 6. v) past or current diagnosis of sleep disorders; vi) habitual use of hypnotics or alcohol at bedtime; vii) subjects engaged in shift-work and vii) failure to complete the questionnaires. The study conformed to the Declaration of Helsinki and all participants provided written informed consent prior to being enrolled in the study.

2.1.1. Psychiatric diagnosis

The assessment of previous and current psychiatric diagnosis according to the criteria of DSM-5 (APA, 2013) was performed using the Structured Clinical Interview for Axis I Disorders (SCID-5) (First et al., 2017). The SCID is constituted by different modules, each of them including specific questions addressed to the detection of diagnostic categories criteria according to DSM-5. Interviews were conducted under the clinical judgment of trained interviewers.

2.1.2. Chronobiological rhythms

Chronobiological rhythms were assessed with the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) (Giglio et al., 2009). The BRIAN contains 21 items designed to assess five domains related to biological rhythms: 1) Sleep (for example: “How is difficult for you to go to sleep and wake up at the same time every day”), 2) Activities (for example “Do you have difficulties to end up your daily activities”), 3) Social aspects (for example “Do you have difficulties to adapt your daily rhythm to that of the others?”), 4) Alimentation (for example “Do you have difficulties to keep a regular timing for your meals?”), based on the last 15 days, and 5) predominant Rhythm (chronotype) based on the last year (for example: “Are you more active or productive during the evening or the morning?”). All items were evaluated on a 4-point scale (1 = not at all, 4 = often). The total score may range from 16 to 84 with higher scores denoting greater disturbance in biological rhythms. The scale has been translated into several languages including Italian (Giglio et al., 2009; Moro et al., 2014). The scale has shown promising validity compared to objective parameters of circadian rhythmicity (Allega et al., 2018).

2.1.3. Emotion regulation

Emotion regulation was evaluated with the Difficulties in Emotion Regulation Scale (DERS) (Gratz, and Roemer, 2004). The DERS is a 36-items and a 5-point scale (raging from 1 – almost never to 5 – almost always). The sum yields a global DERS score ranging from 36 to 180 with higher scores reflecting greater difficulties regulating emotion. The questionnaire includes six subscales 1) Non acceptance of emotion (for example: "When I'm upset, I become angry with myself for feeling that way"), 2) Difficulties engaging in goal-directed behaviors (for example: "When I'm upset, I have difficulty concentrating"), 3) Impulse control difficulties (for example: "I experience my emotions as overwhelming and out of control"), 4) Limited access to effective regulatory strategies (for example: "When I'm upset, I believe that there is nothing I can do to make myself feel better"), 5) Reduced emotional clarity (for example: "I am confused about how I feel", and 6) Lack of emotional awareness (for example: "I pay attention to how I feel" reverse scored). For the Italian version see Sighinolfi et al. (2010).

2.1.4. Psychiatric scales

Depressive symptoms were assessed using the Beck Depression Inventory-II (BDI-II): the BDI-II is a self-report 21-question inventory, and it is one of the most widely used instruments for measuring the severity of depression. The total score ranges from 0–63. According to the authors' recommendations, a BDI-II score > 13 is indicative of depressive symptoms, while moderate/severe depression is indicated by a score of BDI-II > 20 (Beck et al., 1996; Ghisi et al., 2006).

Manic symptoms were assessed with the Young Mania Rating Scale (YMRS). It is an 11-item scale. The clinician rates the severity of the symptoms from 0 (no symptoms/normal behavior) to 4 (extreme deviation) based on the subjective information provided by the patient about the last 48 h and the clinical observation of behavior during the interview. According to the developer of the questionnaire, items 5, 6, 8 and 9 have a double weight for calculating the total score. A YMRS score > 7 is indicative of manic symptoms (Young et al., 1978, Palma and Pancheri, 1999).

Suicidality was evaluated using the Scale for Suicide Ideation (SSI) (Beck et al., 1979). It consists of 19 items that evaluate three dimensions of suicide ideation: active suicidal desire, specific plans for suicide, and passive suicidal desire. Each item is rated on a 3-point scale from 0 to 2. The higher the total score, the greater the severity of suicide ideation. In some previous studies on adult suicidality a score ≥ 6 has been used as a cut off threshold for clinically significant suicidal ideation (Beck et al., 1979; Conti, 1999).

2.2. Statistical analysis

The statistical analyses were performed using NCSS (2008). Results were expressed as Mean ± Standard Deviation (SD). The Shapiro Wilk Test was used to check the normality of the variables. Differences in means between subjects with bipolar disorder and healthy controls were assessed using *t*-tests for normally distributed variables, or the Mann-Whitney U/Wilcoxon Test for non-normally distributed variables. Categorical variables were analyzed via the χ^2 test. Mean p-values were adjusted for the number of tests using the Bonferroni correction with a significance of $p < 0.05$. An a priori power estimation analysis provided a sample size of $n = 35$ with a power of 0.8. A univariate linear regression analysis was performed in order to test direct correlations among the dysregulation of chronobiological rhythms and depressive/manic symptoms, emotion dysregulation and suicidality in a group of subject with bipolar disorder while taking into account current psychiatric comorbidity, current pharmacological treatments, family history for psychiatric disorders and illness duration.

Multiple linear regression models were then built with depressive/manic symptoms, emotion dysregulation and suicidality as dependent variables. In the case of a significant correlation between the values and dependent variables on the univariate analyses, the values were used as independent variables in the multiple linear regression models. All the multiple regression models were checked for multicollinearity. A variable was excluded from the model if it had a variance inflation factor greater than 10 and a condition number greater than 100 in the Eigenvalues of Centered Correlations. A mediation analysis was performed using the Sobel test (Sobel, 1982) with the aim to investigate the potential processes that may underling the relationship between these variables. All pathways of the mediation were tested.

3. Results

3.1. Descriptive statistics

Of the 130 potential participants evaluated, 85 subjects (n°53, 62,4% females, mean age 47.9 ± 12.2 years) met the inclusion/exclusion criteria for Bipolar Disorder type II depressive episode with mixed features. Ten subjects who also suffered for a current substance abuse disorder and 25 subjects who did not complete the evaluations were lastly excluded from the final sample. Thirty-five subjects out of 50 recruited as healthy controls were included in the study for being matched based on gender and age with the group of subjects with bipolar disorder (n° 23, 63,85% famales, mean age 48.4 ± 13). In fact, subjects with bipolar disorder and healthy controls did not differ in terms of gender distribution (χ^2 $p = 0.32$) and mean age ($p = 0.66$). As expected when compared to healthy controls subjects with bipolar disorder showed significantly higher scores on all psychiatric scales such as depressive, manic symptoms and suicidality (Table 1). Individuals with bipolar disorder also showed higher scores on the Biological Rhythms Interview -BRIAN scale with alterations in chronobiological rhythms and on the Difficulties in Emotion Regulation Scale ($p < 0.001$) showing elevated difficulties in emotion regulation when compared to healthy controls.

Table 1
Demographic and psychometric variables.

	Subjects with bipolar disorder (N° = 85)	**Healthy controls** (N° = 35)	**t or χ^2 (df = 2)**	***p***
Age (years) (mean ± SD)	47.9 ± 12.2	48.4 ± 13	0.4	0.663
Gender (females) %	62,4%	63.8%	0.35 [a]	0.884
Illness duration (years) (mean ± SD)	18 ± 11			
Positive family history N° (%)	66(77.6)			
Chronobiological rhythms	mean ± SD	mean ± SD		
BRIAN total score	47.3 ± 9.3	25.6 ± 5.4	4.3	**<0.001**
Emotion regulation	mean ± SD	mean ± SD		
DERS total score	104.8 ± 21.7	83.6 ± 9.2	6.3	**<0.001**
Psychiatric scales	mean ± SD	mean ± SD		
BDI-II total score	22.8 ± 11.8	3.1 ± 1.4	9.7	**<0.001**
YMRS total score	9.2 ± 2.2	3.0 ± 0.1	8.0	**<0.001**
SSI total score	9.2 ± 1.1	0.2 ± 0.5	4.5	**<0.001**
Current drug treatments	N° (%)			
Antidepressants	32(56.8)			
Mood stabilizers	43(55.8)			
Lithium	50(64.9)			
Benzodiazepines	32(56.8)			
Antipsychotics	57(77)			
Anxiety comorbidity	21(17.2)			

Comparison of demographic and clinical features of subjects with bipolar disorder and healthy controls. N = Number, % = percentage, SD: Standard Deviation, **t** = *t* test, **χ^2**:chi square. Legend: BRIAN: Biological Rhythms Interview of Assessment in Neuropsychiatry, DERS:Difficulties in Emotion Regulation Scale, BDI-II: Beck Depression Inventory-II YMRS: Young Mania Rating Scale, SSI: Scale for Suicide Ideation. Significance in bold.

Table 2
Univariate and multivariate regression analyses on depressive and manic symptoms in subjects with bipolar disorder

BDI-II	Univariate		Multivariate		BDI-II	Univariate		Multivariate	
	B	p	B	p		B	p	B	p
BRIAN tot	**0.65**	**<0.001**	**0.53**	**<0.001**	**BRIAN SLEEP**	**1.3**	**<0.001**	0.61	0.077
					BRIAN ACTIVITY	**1.4**	**<0.001**	**1.0**	**0.001**
DERS tot	**0.22**	**<0.001**	**0.11**	**0.032**	**BRIAN SOCIAL**	**1.4**	**0.001**	0.64	0.122
					BRIANALIMENTATION	**1.2**	**0.005**	0.34	0.392
YMRS tot	−0.04	0.814	-	-	**BRIAN RYTHMS**	0.13	0.866	-	-

YMRS	Univariate		Multivariate		YMRS	Univariate		Multivariate	
	B	p	B	p		B	p	B	p
BRIAN tot	0.07	0.264	-	-	**BRIAN SLEEP**	**0.40**	**0.027**	**0.33**	**0.042**
					BRIAN ACTIVITY	0.20	0.203	-	-
DERS tot	0.04	0.198	-	-	**BRIAN SOCIAL**	0.24	0.132	-	-
					BRIANALIMENTATION	0.21	0.157	-	-
BDI-II tot	−0.01	0.814	-	-	**BRIAN RYTHMS**	**0.22**	**0.024**	0.21	0.145

Legend. Results of the univariate and multivariate regression analyses among the BDI-II: Beck Depression Inventory-II (upper part of the table) and of the YMRS: Young Mania Rating Scale and other variables. BRIAN: Biological Rhythms Interview of Assessment in Neuropsychiatry, DERS: Difficulties in Emotion Regulation Scale. The right part of the table shows the results of separate univariate and multivariate regression analyses among the BDI-II: Beck Depression Inventory-II (upper part of the table) and of the YMRS: Young Mania Rating Scale and the BRIAN five areas related to biological rhythms of: Sleep: BRIAN SLEEP, Activity: BRIAN ACTIVITY, Social aspects: BRIAN SOCIAL, Alimentation: BRIAN ALIMENTATION and predominant chronotype: BRIAN RYTHMS. B = unstandardized regression coefficient. Significance in bold.

Table 3
Univariate and multivariate regression analyses on emotion dysregulation in subjects with bipolar disorder

DERS	Univariate		Multivariate		DERS	Univariate		Multivariate	
	B	p	B	p		B	p	B	p
BRIAN tot	**1.1**	**<.001**	**0.77**	**0.002**	**BRIAN SLEEP**	**2.3**	**<0.001**	1.1	0.112
					BRIAN ACTIVITY	**2.3**	**<0.001**	**1.8**	**0.005**
YMRS tot	0.09	0.808	-	-	**BRIAN SOCIAL**	**1.8**	**0.022**	0.31	0.717
					BRIANALIMENTATION	**2.0**	**0.015**	0.70	0.334
BDI-II tot	**0.85**	**<.001**	**0.50**	**0.015**	**BRIAN RYTHMS**	**2.1**	**<0.001**	**3.7**	**0.022**

Legend. Results of the univariate and multivariate regression analyses among the DERS: Difficulties in Emotion Regulation Scale and other variables. BRIAN: Biological Rhythms Interview of Assessment in Neuropsychiatry, BDI-II: Beck Depression Inventory-II, YMRS: Young Mania Rating Scale. The right part of the table shows the results of separate univariate and multivariate regression analyses among the DERS: Difficulties in Emotion Regulation Scale and the BRIAN five areas related to biological rhythms of: Sleep: BRIAN SLEEP, Activity: BRIAN ACTIVITY, Social aspects: BRIAN SOCIAL, Alimentation: BRIAN ALIMENTATION and predominant chronotype: BRIAN RYTHMS. B = unstandardized regression coefficient. Significance in bold.

3.2. Correlations between variables

3.2.1. Determinants of depressive and manic symptoms

The univariate analysis in the group of healthy controls showed no correlation between depressive symptoms expressed by BDI-II and manic symptoms expressed by YMRS and the variables considered (respectively BRIAN-BDI-II: coeff. = 0.15, $p = 0.423$; YMRS-BDI-II: coeff. = −0.22, $p = 0.254$; DERS-BDI-II: coeff. = 0.25, $p = 0.333$; BRIAN-YMRS: coeff. = 0.12, $p = 0.434$; DERS-YMRS: coeff. = 0.11, $p = 0.355$).

The univariate analysis in subjects with bipolar disorder showed a positive correlation between depressive symptoms and both alterations in emotion regulation and chronobiological rhythms (Table 2). Particularly, alterations in sleep/wake pattern, activities, social aspects and alimentation significantly predicted depressive symptoms (Table 2). No correlations were found among depressive symptoms and other variables considered.

The multiple-regression model including depressive symptoms as the dependent variable, both chronobiological rhythms and emotion alterations as independent variables, was significant ($F = 20.2$, $p = < 0.001$). Both variables remained related to depressive symptoms. (Table 2). Among the BRIAN areas the dis- rhythmicity of activities was the one most closely related to depressive symptoms.

The univariate analysis in subjects with bipolar disorder showed no correlations between manic symptoms and both emotion and chronobiological rhythms alterations when considering the BRIAN total score (Table 2). Manic symptoms were related to the chronobiological dis-rhythmicity of both BRIAN areas sleep/wake pattern and chronotype. No correlations were found among manic symptoms and other variables considered.

3.2.2. Determinants of emotion dysregulation

The univariate analysis in the group of healthy controls showed no correlation between emotion regulation expressed by DERS and the variables considered (coeff = unstandardized coefficient: BRIAN: coeff. = 0.31, $p = 0.763$; BDI-II: coeff. = −0.22, $p = 0.252$; YMRS: coeff. = 0.42, $p = 0.134$).

The univariate analysis in subjects with bipolar disorder showed a positive correlation between emotion dysregulation and chronobiological rhythms alteration, and depressive symptoms (Table 2). Particularly, alterations in each areas of the chronobiological rhythms scale such as sleep, activities, social aspects, alimentation and disturbed chronotype significantly predicted emotion dysregulations (Table 3). No correlations with other variables considered were found.

The multiple-regression model including emotion dysregulation as the dependent variable, chronobiological rhythms alterations and depressive symptoms as independent variables, was significant ($F = 17.8$, $p = < 0.0001$). Both variables remained related to emotion dysregulation (Table 3). Emotion dysregulation was related to the chronobiological dis- rhythmicity of the pattern of daily activities among BRIAN areas.

Table 4
Univariate and multivariate regression analyses on suicidality in subjects with bipolar disorder

SSI	Univariate		Multivariate		SSI	Univariate	
	B	p	B	p		B	p
BRIAN tot	**0.16**	**0.012**	0.007	0.821	**BRIAN SLEEP**	0.21	0.25
					BRIAN ACTIVITY	0.24	0.11
YMRS tot	**0.23**	**0.024**	0.08	0.062	**BRIAN SOCIAL**	**0.65**	**0.003**
					BRIAN ALIMENTATION	0.31	0.16
BDI-II tot	**0.12**	**0.013**	0.02	0.335	**BRIAN RYTHMS**	0.11	0.78
DERS tot	**0.06**	**0.035**	0.01	0.193			
No Lithium	**0.97**	**0.044**	**1.2**	**0.024**			

Legend. Results of the univariate and multivariate regression analyses among the SIS: Scale for Suicide Ideation and other variables. BRIAN: Biological Rhythms Interview of Assessment in Neuropsychiatry, BDI-II: Beck Depression Inventory-II, YMRS: Young Mania Rating Scale, DERS: Difficulties in Emotion Regulation Scale. The right part of the table shows results of separate univariate and multivariate regression analyses among the SIS: Scale for Suicide Ideation and the BRIAN five areas related to biological rhythms of: Sleep: BRIAN SLEEP, Activity: BRIAN ACTIVITY, Social aspects: BRIAN SOCIAL, Alimentation: BRIAN ALIMENTATION and predominant chronotype: BRIAN RYTHMS. No lithium = absence of lithium in the therapy. B = unstandardized regression coefficient. Significance in bold.

3.2.3. Determinants of suicidality

The univariate analysis in the group of healthy controls showed no correlation between suicidality expressed by SIS and the variables considered (coeff = unstandardized coefficient: BRIAN: coeff. = 0.32, $p = 0.424$; BDI-II: coeff. = 0.08, $p = 0.335$; YMRS: coeff. = 0.07, $p = 0.125$, DERS: coeff. = −0.33, $p = 0.556$).

The univariate analysis in subjects with bipolar disorder showed a positive correlation between suicidality depressive and manic symptoms, emotion dysregulation and chronobiological rhythms alterations (Table 4). Particularly a relationship was found with alterations in the rhythmicity of social aspects (Table 4). A significant correlation was found between higher SSI scores and the absence of lithium in the therapy. No correlations were found between suicidality and other variables considered.

The multiple-regression model including suicidality as the dependent variable, chronobiological rhythms alterations and manic /depressive symptoms, emotion dysregulations and the absence of lithium in the therapy as independent variables, was significant ($F = 24.5$, $p = < 0.0001$) only the absence of lithium in the therapy remained the significant variable.

3.2.4. Mediation analyses

The hypothesis of the study was also to investigate the potential processes that underling the association between variables. We tested all mediations pathways. In particular, a mediation analysis was conducted with emotion dysregulation (DERS totals score) as the mediator between chronobiological rhythm alterations (BRIAN total score) and depressive symptoms (BDI-II total score). It revealed a mediation effect of emotion dysregulation in the relationship between chronobiological dis-rhythmicity and depressive symptoms (Fig. 1, mediated effect = 3.25, $p = 0.001$). Emotion dysregulation also mediated the association between the dis-rhythmicity of social aspects (BRIAN social) and suicidality (SSI total score) (Fig. 1 mediated effect = 2.52, $p = 0.011$). Non other mediation analyses resulted significant.

4. Discussion

We assessed a sample of subjects with bipolar disorder II depressive episode with mixed features and a group of healthy controls by evaluating circadian rhythm alterations with the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) (Giglio et al., 2009). Our aim was to assess their potential association with emotion dysregulation and suicidality in bipolar individuals, while taking into account depressive/manic symptoms, current pharmacological therapy and other clinical/demographic factors that may contribute to mood disorders.

Our results support the view that subjects with bipolar disorder have a dysregulation in chonobiological rhythms correlated with depressive-manic symptoms, emotion dysregulation and suicidality. Particularly the dis-rhythmicity of daily activities was related to depressive symptoms and to emotion dysregulation while manic symptoms were related to the dis-rhythmicity of the sleep/wake pattern and suicidality to the dis-rhythmicity of social aspects.

In our sample, alteration in chonobiological rhythms was significantly higher in subjects with bipolar disorder than in healthy controls thus confirming previous reports of population-based studies (Duarte Faria et al., 2015; Mondin et al., 2017) and of studies interesting bipolar individuals during remission phases (Rosa et al., 2013; Iyer and Palaniappan, 2017) or inserted in mood disorders programmes (Giglio et al., 2010; Pinho et al., 2016). Subject with bipolar disorder also showed greater difficulties with emotion regulation when compared to healthy controls confirming previous hypothesis (Hoffman et al., 2012; Henry et al., 2012).

In subject with bipolar disorder, depressive/manic symptoms were not only related to emotion dysregulation confirming previous reports (Visted et al., 2018), but also to chonobiological rhythm alterations as previously observed (Pinho et al., 2016; Mondin et al., 2017). In particular depressive symptoms were related to the dis-rhythmicity of daily activities while manic symptoms resulted related to alterations in the rhythmicity of the sleep/wake pattern.

As expected emotion dysregulation resulted correlated not only with depressive symptoms (Visted et al., 2018) but also with chonobiological rhythm alterations; in particular difficulties in impulse control, in engaging in goal-directed behaviors and in the access to effective regulatory strategies were related to chonobiological rhythm alterations. Similarly, suicidality was related not only to mood and emotion dysregulation as previously observed (Johnson et al., 2017), and to the absence of lithium in the therapy confirming previous reports (Benard et al., 2016), but also to chonobiological rhythm alterations. In particular, suicidality was related to the dis-rhythmicity of social patterns. Although, when considering the absence of lithium in the therapy this was the factor more strongly related to suicidality. Conversely, all these correlations were not observed in healthy controls. Results of the mediation analyses showed that emotion dysregulation may mediate the relationship between chonobiological dis-rhythmicity and bipolar symptomatology, especially depressive symptoms and suicidality.

Therefore, we could hypothesize a complex interplay between chonobiological alterations mood and emotion dysregulation. According to recent theories (McClung, 2013; Vadnie and McClung, 2017) chonobiological dis-rhythms may contribute to mood disorders by dysregulating most of the systems involved in mood and emotion regulation, contributing to the insurgence and the chronicization of mood disorders.

The evaluation of the different aspects of circadian rhythmicity including the sleep/wake pattern, daily activities, social aspects, alimentation and prevalent chronotype should be included in the routinary clinical evaluation of bipolar patients. It has already been suggested that chronobiological intervention may help provide preventive strategies and/or improve the treatment of mood disorders (Harvey, 2008; Mondin et al., 2015; Dellaspezia and Benedetti, 2015). We may hypothesized that by re-synchronizing chonobiological rhythms we may improve the regulation of mood, emotions and suicide ideation.

These results should be interpreted in light of several limitations including the lack of physiological measures of chonobiological

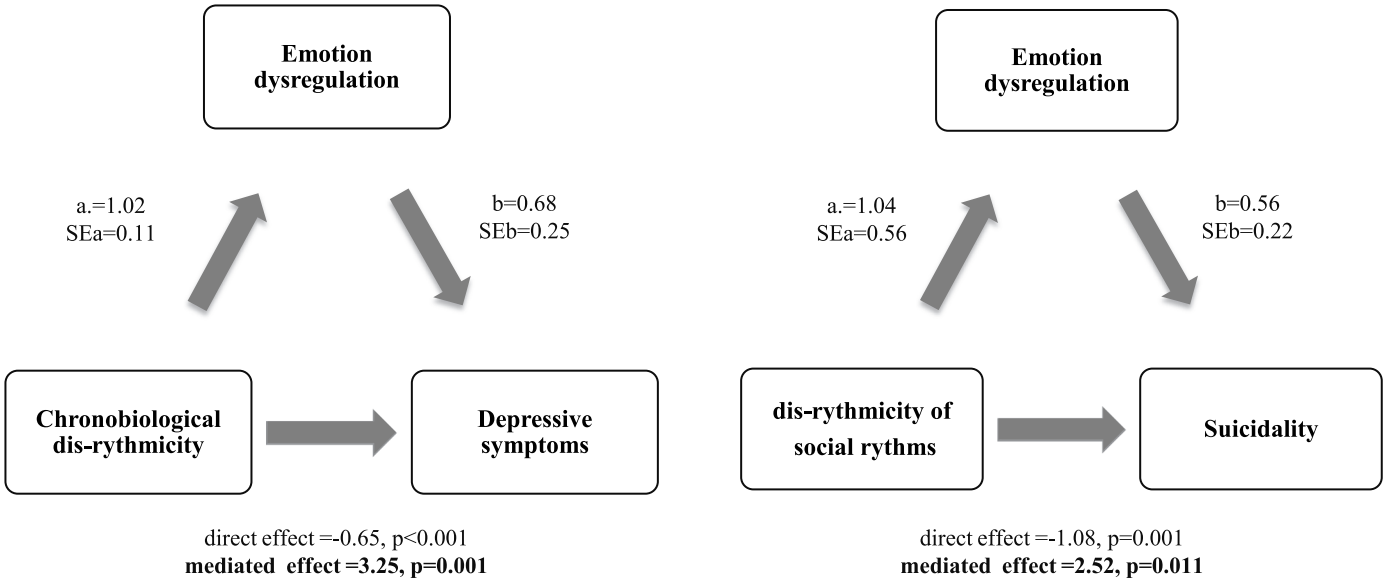

Fig. 1. Mediation analyses Emotion dysregulation mediates the association between chronobiological dis-rhythmicity and depressive symptoms, and between the dis-rhythmicity of social aspects and suicidality. a: unstandardized regression coefficient for the association between the independent variable and mediator, SEa = standard error of a. b: coefficient for the association between the mediator (in presence of independent variable) and the dependent variable, SEb = standard error of b. Mediated effect = Sobel test value. Significance in bold.

rhythms. Secondly, despite the use of mediation analyses, the cross-sectional design of the study limits any causal interpretation. Consequently, longitudinal studies are needed with larger samples of subjects with bipolar disorder and other types of mood disorders to examine the direction of risk and generalizability of the current findings. Future studies should also take into account not only the current pharmacological therapy but also the drug treatment history including the duration of the lithium therapy and serum lithium levels.

Since an association between emotional affective temperaments and alterations in chronotype has been shown in non-clinical population (Ottoni et al., 2012), future studies should also include the evaluation of affective temperaments and the investigation of their association with chronotypes and emotion regulation in subjects with bipolar disorder.

In conclusion, this study suggests that: i) subjects with bipolar disorder show a chronobiological dis-rhythmicity which may interest various areas of life including the pattern of sleep/wake, activities, social life, alimentation and chronotype ii) these different aspects of chronobiological dis-rhythmicity may be related to mood swings, emotion dysregulation and suicidality. These findings may have clinical implications. In particular it emerges that the assessment of chronobiological rhythms in bipolar individuals should be a priority in order to identify those who may benefit from prevention and early chronobiological intervention strategies.

Conflict of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. No conflict of interests to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.11.056.

References

Abreu, T., Bragança, M., 2015. The bipolarity of light and dark: a review on bipolar disorder and circadian cycles. J. Affect. Disord. 185, 219–229.
Adan, A., Archer, S.N., Hidalgo, M.P., 2012. Circadian typology: a comprehensive review. Chronobiol. Int. 29, 1153–1175.
Allega, O.R., Leng, X., Vaccarino, A., Skelly, M., Hidalgo, M.P., Soares, C.N., Kennedy, S.H., Frey, B.,N., 2018. Performance of the biological rhythms interview for assessment in neuropsychiatry: an item response theory and actigraphy analysis. J. Affect. Disord. 1 (225), 54–63.
Alloy, L.B., Ng, T.H., Titone, M.K., Boland, E.M., 2017. Circadian rhythm dysregulation in bipolar spectrum disorders. Curr. Psychiatry Rep. 19, 21.
American Psychiatric, Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, Fifth edition. American Psychiatric Pub, Washington DSM-5.
Beck, A.T., Kovacs, M., Weissman, A., 1979. Assessment of suicidal intention: the scale for suicide ideation. J. Consult. Clin. Psychol. 47, 343.
Beck, A.T., Steer, R.A., Ball, R., Ranieri, W., 1996. Comparison of beck depression inventories -IA and -II in psychiatric outpatients. J. Pers. Assess. 67, 588–597.
Benard, V., Vaiva, G., Masson, M., Geoffroy, P.,A., 2016. Lithium and suicide prevention in bipolar disorder. Encephale 42, 234–241.
Conti, L., 1999. Repertorio delle scale di valutazione in psichiatria. SEE Firenze.
Cretu, J.B., Culver, J.L., Goffin, K.C., Shah, S., Ketter, T.A., 2016. Sleep, residual mood symptoms, and time to relapse in recovered patients with bipolar disorder. J. Affect. Disord. 190, 162–166.
Dallaspezia, S., Benedetti, F., 2015. Chronobiology of bipolar disorder: therapeutic implication. Curr. Psychiatry Rep. 17, 606.
Duarte Faria, A., Cardoso, T.A., Campos Mondin, T., Souza, L.D., Magalhaes, P.V., Patrick Zeni, C., Silva, R.A., Kapczinski, F., Jansen, K., 2015. Biological rhythms in bipolar and depressive disorders: a community study with drug-naïve young adults. J. Affect. Disord. 1 (186), 145–148.
Ferrari, A.J., Norman, R.E., Freedman, G., Baxter, A.J., Pirkis, J.E., Harris, M.G., Page, A., Carnahan, E., Degenhardt, L., Vos, T., Whiteford, H.A., 2014. The burden attributable to mental and substance use disorders as risk factors for suicide: findings from the global burden of disease study 2010. PLoS One 9, 91936.
First, M.B., Williams, J.B.W., Karg, R.S., Spitzer, R.L., 2017. SCID-5-CV. Intervista Clinica Strutturata per i Disturbi del DSM-5. Versione Per Il Clinico. Ed. Italiana a cura Di Andrea Fossati e Serena Borroni. Raffaello Cortina Editore, Milano.
Ghisi, M., Flebus, G.B., Montano, A., Sanavio, E., Sica, C., 2006. Beck Depression Inventory-II. Manuale italiano, Firenze Giunti Editore.
Giglio, L.M., Magalhães, P.V., Andreazza, A.C., Walz, J.C., Jakobson, L., Rucci, P., Rosa, A.R., Hidalgo, M.P., Vieta, E., Kapczinski, F., 2009. Development and use of a biological rhythm interview. J. Affect. Disord. 118, 161–165.
Giglio, L.M., Magalhães, P.V., Andersen, M.L., Walz, J.C., Jakobson, L., Kapczinski, F., 2010. Sleep Breath. 14, 153–155.
Gratz, K.L., Roemer, L., 2004. Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation of the difficulties in emotion regulation scale. J. Psychopathol. Behav. Assess. 30, 315.
Gross, J.J., Thompson, R.A., 2011. Emotion regulation: conceptual foundations. In: Gross, J J (Ed.), Handbook of Emotion Regulation. Guilford Press, New York, NY, USA.
Harvey, A.G., 2008. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. Am. J. Psychiatry 165, 820–829.
Harvey, A.G., 2011. Sleep and circadian functioning: critical mechanisms in the mood disorders? Annu. Rev. Clin. Psychol. 7, 297–319.
Henry, C., Phillips, M., Leibenluft, E., M'Bailara, K., Houenou, J., Leboyer, M., 2012. Emotional dysfunction as a marker of bipolar disorders. Front. Biosci. 4, 2622–2630.
Hofmann, S.G., Sawyer, A.T., Fang, A., Asnaani, A., 2012. Emotion dysregulation model of mood and anxiety disorders. Depress. Anxiety 29, 409–416.
Isometsä, E., 2014. Suicidal behaviour in mood disorders–who, when, and why? Can. J. Psychiatry 59, 120–130.
Iyer, A., Palaniappan, P., 2017. Biological dysrhythm in remitted bipolar I disorder. Asian J. Psychiatr. 30, 218–224.
Johnson, S.L., Carver, C.S., Tharp, J.A., 2017. Suicidality in bipolar disorder: the role of emotion-triggered impulsivity. Suicide Life Threat Behav. 47, 177–192.
Kanady, J.C., Soehnera, A.M., Harvey, A.G., 2015. A retrospective examination of sleep disturbance across the course of bipolar disorder. J. Sleep. Disord. Ther. 4.
Kupfer, D.J., Frank, E., Phillips, M.L., 2012. Major depressive disorder: new clinical, neurobiological, and treatment perspectives. Lancet 379, 1045–1055.
McClung, C.A., 2013. How might circadian rhythms control mood? Let me count the ways... Biol. Psychiatry. 74, 242–249.
Measso, G., Cavarzeran, F., Zappalà, G., 1993. Dev. Neuropsychol. 9, 77–85.
Milhiet, V., Boudebesse, C., Bellivier, F., 2014. Circadian abnormalities as markers of susceptibility in bipolar disorders. Front Biosci. (Schol. Ed.) 6, 120–137.
Mondin, T.C., Cardoso, T.A., Jansen, K., Silva Gdel, G., Souza, L.D., Silva, R.A., 2015. Long-term effects of cognitive therapy on biological rhythms and depressive symptoms: a randomized clinical trial. J. Affect. Disord. 187, 1–9.
Mondin, T.C., Cardoso, T.A., Souza, L.D.M., Jansen, K., da Silva Magalhães, P.V., Kapczinski, F., da Silva, R.A., 2017. Mood disorders and biological rhythms in young adults: a large population-based study. J. Psychiatr. Res. 84, 98–104.
Moro, M.F., Carta, M.G., Pintus, M., Pintus, E., Melis, R., Kapczinski, F., Vieta, E., Colom, F., 2014. Validation of the Italian Version of the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN): some considerations on its screening usefulness. Clin. Pract. Epidemiol. Ment. Health 13 (10), 48–52.
Ottoni, G.L., Antoniolli, E., Lara, D.R., 2012. Circadian preference is associated with emotional and affective temperaments. Chronobiol. Int. 29, 786–793.
Palma, A., Pancheri, P., 1999. Scale di valutazione e di misura dei sintomi psichiatrici. In: Cassano, G.B., Pancheri, P. (Eds.), Trattato Italiano di Psichiatria, Seconda edizione. Masson Italia, Milano.
Pinho, M., Sehmbi, M., Cudney, L.E., Kauer-Sant'anna, M., Magalhães, P.V., Reinares, M., Bonnín, C.M., Sassi, R.B., Kapczinski, F., Colom, F., Vieta, E., Frey, B.N., Rosa, A.R., 2016. The association between biological rhythms, depression, and functioning in bipolar disorder: a large multi-center study. Acta Psychiatr. Scand. 133, 102–108.
Rosa, A.R., Comes, M., Torrent, C., Solè, B., Reinares, M., Pachiarotti, I., Salamero, M., Kapczinski, F., Colom, F., Vieta, E., 2013. Biological rhythm disturbance in remitted bipolar patients. Int. J Bipolar Disord. 1, 6.
Schaffer, A., Isometsä, E.T., Tondo, L., Moreno, H., Turecki, G., Reis, C., 2015. International Society for Bipolar Disorders Task Force on Suicide: meta-analyses and meta-regression of correlates of suicide attempts and suicide deaths in bipolar disorder. Bipolar Disord. 17, 1–6.
Sighinolfi, C., Norcini Pala, A., Rocco Chiri, L., Marchetti, I., Sica, C., 2010. Difficulties in Emotion Regulation Scale (DERS): Traduzione e adattamento italiano. Psicoterapia Cognitiva e Comportamentale 1, 1–44.
Sobel, M.E., 1982. Asymptotic confidence intervals for indirect effects in structural equation models. Sociol. Methodol. 13, 290–312.
Vadnie, C.A., McClung, C.A., 2017. Circadian rhythm disturbances in mood disorders: insights into the role of the suprachiasmatic nucleus. Neural. Plast. 2017, 1504507.
Visted, E., Vøllestad, J., Nielsen, M.,B., Schanche, E., 2018. Emotion regulation in current and remitted depression: a systematic review and meta-analysis. Front. Psychol. 9, 756.
Whiteford, H.A., Degenhardt, L., Rehm, J., Baxter, A.J., Ferrari, A.J., Erskine, H.E., 2013. Global burden of disease attributable to mental and substance use disorders: findings from the global burden of disease study 2010. Lancet 382, 1575–1586.
Wessa, M., Linke, J., 2009. Emotional processing in bipolar disorder: behavioural and neuroimaging findings. J. Int. Rev. Psychiatry 21, 357–367.
Wittchen, H.U., 2012. The burden of mood disorders. Science 338, 15.
Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiat. 133, 429.