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RESEARCH PAPER

CIRCADIAN RHYTHM ALTERATIONS MAY BE RELATED TO IMPAIRED RESILIENCE, EMOTIONAL DYSREGULATION AND TO THE SEVERITY OF MOOD FEATURES IN BIPOLAR I AND II DISORDERS

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Abstract

Objective: The study aimed to investigate the possible impact of resilience and emotion dysregulation on the clinical manifestations of bipolar disorders (BDs) focusing on the possible role of circadian rhythm alterations.

Method: A sample of 197 inpatients suffering from BD of type I (BDI) or II (BDII) were assessed during a major depressive episode using the Structural Clinical Interview for DSM-5 (SCID-5), the Beck Depression Inventory-II (BDI-II), the Young Mania Rating Scale (YMRS), Resilience Scale for Adults (RSA), Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN), Difficulties in Emotion Regulation Scale (DERS) and the Scale for Suicide Ideation (SSI). Participants with or without circadian rhythm disturbances as measured with Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN), were compared; regression and mediation analyses were computed.

Results: Participants with circadian rhythms disturbances showed a greater severity of depressive symptoms, of suicidal risk, lower resilience and more disturbances in emotion regulation including impulsivity and regulatory strategies. The logistic regression revealed that circadian rhythm disturbances was related to depressive symptoms (O.R. 4.0), suicidal risk (OR 2.51), emotion dysregulation (OR 2.28) and low resilience (OR 2.72). At the mediation analyses, circadian rhythm alterations showed an indirect effect on depressive symptoms by impairing resilience (Z= 3.17, p=0.0014)/ emotional regulation (Z= 4.36, p<0.001) and on suicidal risk by affecting resilience (Z= 2.00, p=0.045) and favoring impulsivity (Z= 2.14, p=0.032).

Conclusions: The present findings may show that circadian rhythm alterations might play a key role in BD manifestations, as being correlated with more severe clinical presentations of depressive symptoms, suicidal risk, impaired resilience and emotional regulation. Addressing circadian rhythm alterations might potentially promote resilience and emotion regulation hence improving mood symptoms and suicidal risk in BDs.

Key words: bipolar disorder, resilience, mood symptoms, circadian rhythms, emotion dysregulation, impulsivity, suicidal risk

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Introduction

Bipolar disorders (BDs) are among the most prevalent and the most likely to be recurrent, chronic and disabling psychiatric conditions (Ferrari et al., 2016; Vieta et al., 2018), while leading to global burdens of disease in terms of disability, morbidity, premature mortality and to a significant suicidal risk (Delgado, 2015; Hayes et al., 2015; Ferrari et al., 2016; Vieta et al., 2018; Miller & Black, 2020). They are complex disorders resulting from the interaction of genetic, physiological, psychological, and environmental factors (Vieta et al., 2018). The different combinations of these factors may lead to a spectrum of acute clinical manifestations including elevated mood such as mania or hypomania, depressed mood or the co-occurrence of them, with high variability and magnitude among patients (Delgado, 2015). The understanding of the factors involved in BDs and their mood episode recurrences should thus be considered as a priority to identify potential early markers that could

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help in improving and personalizing treatment strategies.

Within this framework, circadian rhythm disturbances might be proposed as a potentially modifiable marker in BDs. Compelling evidence suggested that mood disorders are frequently associated with dysfunctions of the biological clock that, according to the "circadian hypothesis of mood disorders" may constitutes a hallmark of BDs (Maruani et al., 2018). The majority of individuals with BDs presents alterations in the circadian rhythmicity in physiological and behavioral timekeeping processes including social life, activities, eating and sleep/wake patterns, prior and during the depressive or manic episodes, as well as during euthymia as well (Vadnie & McClung, 2017; Geoffroy, 2018; Maruani et al., 2018; Geoffroy & Palagini, 2021). Irregular and delayed sleep patterns are frequent across mood episodes and inter-episode periods of BD (Geoffroy et al., 2015). Circadian rhythms dysregulation, in particular the de-synchronization of sleep and social life, has been associated with the severity of mood symptoms, insomnia symptoms, emotional dysregulation, and suicidal behaviors in BDs (Takaesu et al., 2018; Gonzalez & Tohen, 2018; Palagini et al., 2019; Benard et al., 2019; Palagini et al., 2021). In this context, recent international guidelines have indicated a specific efficacy of chronotherapeutics targeting these circadian alterations during all phases of BDs (Gottlieb et al., 2019). As such circadian rhythm alterations may represent early modifiable markers that could help in improving treatment strategies in BDs.

Among important factors contributing to BDs, the stress vulnerability/resilience dimension may play a key role (Kapczinski et al., 2008). Indeed, stress/episode-induced changes in brain regions involved in stress system may lead to cumulative build-up of allostatic overload which would render patients less resilient and more vulnerable to subsequent environmental stressors and episodes (Kapczinski et al., 2008). In particular, resilience is a modifiable stress-risk dimension process influenced by a variety of genetic, epigenetic, developmental, psychological, and environmental factors, that determines an individual's capacity to adapt successfully to stressful events (Hjemdal et al., 2006). Factors composing resilience include characteristics and resources of the individual and external factors such as supportive family environment and external social networks that support and reinforce (Hjemdal et al., 2006). Higher levels of resilience have been related to less depressive symptomatology (Wermelinger Ávila et al., 2017), and may be a protective factor against suicidal risk (Liu et al., 2014).

On the other hand, low resilience has been associated with a dysregulation in emotions and stress response possibly involved in psychopathological process of BDs (Choi et al., 2015), as well as to emotional impulsivity, internalized stigma, poorer cognitive functions, and reduced quality of life in these psychopathological conditions (Nunes & Rocha, 2022), and increased suicidal risk in psychiatric populations (Roy et al., 2007).

Emotion dysregulation—which refers to the inappropriate shaping of emotion based on context, goals, or demands—may affect resilience being a critical component in the development and maintenance of BDs (Townsend & Altshuler, 2012). Several neurobiological studies examined the link between emotional dysregulation and mood disorders showing a dysfunction in the brain circuitry regulating emotions in BDs (Townsend & Altshuler, 2012; Wessa et al., 2014). Recent theories (Vadnie et al., 2017; Geoffroy, 2018; Wirz-Justice & Benedetti, 2020*)* hypothesized that chonobiological dis-rhythmicity might contribute to mood disorders by dysregulating most of the systems involved in mood and emotion regulation. In particular, the key role of sleep in regulating stress system and emotions has been hypothesized (Walker, 2009; Lo Martire et al., 2020). In this framework, while circadian sleep disturbances might be plausibily linked to emotion dysregulation and low resilience in BDs, very few studies evaluated their association with mood symptoms in BDs (Palagini et al., 2019). Finally, whereas risk factors for suicide are multiple and complex, the desynchronization of circadian rhythms may be plausibly also related to risk of suicidal behaviors in BD (Palagini et al., 2021), in particular contributing to the dysregulation of stress system and emotions (Palagini et al., 2019; Benard et al., 2019; Palagini et al., 2021). Althought these circadian rhythm alterations may be related to some factors contributing to suicidal risk such as impulsivity and hopelessness (Palagini et al.,2019; Palagini et al., 2021), few studies have evaluated other potential links including those with emotion dysregulation and levels of resilience.

Therefore, in this context of a paucity of research examining relationships among circadian rhythm disturbances, resilience, and emotion dysregulation in BDs, we aimed to explore how these factors might be interrelated and collectively associated with mood features and suicidal risk in a population of patients suffering from BD I or BD II during a major depressive episode, with and without circadian sleep disturbances.

Methods

a) Subjects

A consecutive series of inpatients hospitalized at the psychiatric ward of the Azienda Ospedaliero-Universitaria Pisana (AUOP, University of Pisa, Italy), with a diagnosis of BDI or BDII, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (2013) criteria for a major depressive episode, were included in the present study.

Inclusion criteria were: participants with 1) a current diagnosis of major depressive episode with or without mixed features in the context of BDI or BDII 2) who were between 18 and 65 years of age and, 3) who provided informed consent to participate in the study.

Exclusion criteria were: 1) a current or lifetime diagnosis of substance use disorder, 2) a current depressive episode with psychotic features, 3) other subtypes of BD (i.e. not other specified according to DSM-5), 4) a cognitive impairment, as assessed with the Mini Mental State Evaluation with a cut-off score <24 (for the Italian version) (Measso et al., 1993).

The current study was a cross-sectional observational study approved by the local ethical committee (protocol number: 12390) as a part of an ongoing main research plan aimed at characterizing insomnia and chrono-biological rhythms in several types of mood disorders. The study conformed to the Declaration of Helsinki and all participants provided written informed consent prior to being enrolled in the study.

b) Clinical assessment

All participants were evaluated with a set of questionnaires including the Structured Clinical Interview for DSM-5 (SCID-5) (First et al., 2017) to assess the presence of current or lifetime psychiatric diagnoses, the Italian version of Resilience Scale for Adults (RSA) (Capanna et al., 2015), 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 & Roemer, 2004; Sighinolfi et al., 2010) to evaluate emotion dysregulation, the Scale for Suicide Ideation (SSI) (Beck et al., 1979) to evaluate suicidal ideation and preparatory behaviors. Since previous studies on circadian rhythms dysregulation using BRIAN determined a cut off threshold of 40 for the diagnosis of Delayed Sleep Wake Phase Disorders (Kanda et al., 2021), we compared bipolar patients with (BRIAN total score>40) and without (BRIAN total score <40) circadian rhythm alterations accordingly.

The Beck Depression Inventory- II (BDI-II) (Beck, et al. 1996) was used to evaluate depressive symptoms, mixed features were diagnosed using the SCID-5 (First et al., 2017), and manic symptoms were evaluated with the Young Mania Rating Scale (YMRS) (Young et al., 1978). All the participants also completed clinical report forms that included current pharmacological treatments.

c) Assessment scales

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) Activity (for example: *"Do you have difficulties to end up your daily activities"*); 3) Social aspect (for example: *"Do you have difficulties to adapt your daily rhythm to that of the others?*"); 4) Eating pattern (for example: *"Do you have difficulties to keep a regular timing for your meals?"*), based on the subjective information provided by the patient about the last 15 days; and 5) the 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 is recommended by the international societies for BD as a self-report measurement for circadian function in BD (Murray et al., 2020), and it has shown promising validity compared to objective parameters of circadian rhythmicity (Murray et al., 2020). A score of 40 points provided a sensitivity of 80.0% and a specificity of 75.6% for the positivity of Delayed Sleep-Wake Phase Disorders (Kanda et al., 2021).

The RSA (Capanna et al., 2015) is a 33 item self-report scale for adults to measure six resilience factors and a total score. Participants answer on a 7-point semantic differential scale in which each item has a positive and a negative attribute at each end of the scale continuum. Scores vary between 33 and 231, with higher scores indicating higher levels of resilience. The scale consists of 6 subscales measuring individual's characteristics in: 1) Perception of Self: concerning the confidence in own abilities, self-confidence, self-efficacy (for example: *"No matter what happens I always find a solution"*); 2) Planned Future: concerning the ability to plan ahead and formulate clear goals (for example: *"my projects for the future are easy to realize"*); 3) Social Competence concerning individual's own perception of social competence (for example: *"It is important for me to be flexible in social circumstances"*); 4) Structured Style: concerning goal oriented, planning ability, organization of own time, routine oriented (for example: *"Rules and regular routines make my daily life easier"*); external factors, such as 5) Family Cohesion: concerning shared values, cohesion, loyalty, mutual appreciation, (for example: *"There are strong bonds in my family"*); 6) Social Resources: concerning social support (for example: *"I always have someone who can help me when needed"*). For the Italian version, see Capanna et al. (2015).

The DERS is a 36-item scale. When responding to the DERS, subjects were asked to indicate the degree to which the statements of the questionnaire may apply to them by selecting an appropriate rating on a 6-point scale ranging 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*"); 4) reduced emotional clarity (for example: "*I am confused about how I feel*"); 6) a lack of emotional awareness (for example: "*I pay attention to how I feel*", reverse scored). For the Italian version, see Sighinolfi et al. (2010).

The Scale for Suicide Ideation (SSI) evaluates suicidal ideation and behaviors. It is a clinician-rating scale and is presented in a semi-structured interview format (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 Beck Depression Inventory-II (BDI-II) is a self-report 21-question inventory to assess depressive symptoms. The total score ranges from 0–63. A BDI-II total score of > 13 is indicative of depressive symptoms (Beck et al., 1996).

The Young Mania Rating Scale (YMRS) is commonly employed to assess manic symptoms. An YMRS total score of > 7 is indicative of hypomanic/manic symptoms (Young et al., 1978).

Statistical analysis

The statistical analyses were performed using SPSS 22.0 for Windows. Results were expressed as mean ± standard deviation (SD) and/or percent values. The Shapiro-Wilk Test was used to check the normality of the variables. Differences in means between participants with circadian rhythms disorder BRIAN >40 and participants with non circadian rhythm disorders BRIAN≤40 were assessed by Student t-tests for normally distributed variables, or the Mann-Whitney U/Wilcoxon Test for non-normally distributed variables. Categorical variables were analyzed via the Chi-Squared Test.

For the purpose of the study, we conducted analyses taking into account in addition BRIAN total score and the score of BRIAN each domain. Correlations between continuous variables were tested using the Spearman rho correlation for non-normally distributed variables and using Pearson correlations index for normally distributed variables. Linear and multiple regression and logistic models were then built with depressive/manic symptoms and suicidal ideation and behaviors as dependent variables while taking into account, current

pharmacological treatments, previous suicidal attempts and illness duration. 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 using the Sobel Test (Sobel, 1982) was performed in order to study the potential processes that may underlie the relationships between these variables. All pathways of the mediation were tested.

Results

a) Clinical Characteristics

From the 240 patients, 29 were excluded due to comorbid substance use disorder or concomitant psychotic features, and 24 were excluded due to incomplete questionnaires. Of the 197 patients included, 84 (42.6%) participants were women, (mean age 46.4±13 years) and 113 were men (57.4%).

Ninety-six patients (48.7%) met the inclusion/exclusion criteria for BDI and 101 (51.3%) for BD II, while 118 (59.9%) had mixed features. No patients met criteria for a formal lifetime or current post-traumatic stress disorder (PTSD), but 61(34.9%) met criteria for other anxiety disorders, of whom 40 participants had panic disorder and 21 had generalized anxiety disorder.

One hundred and eighteen subjects (60%) showed circadian rhythm disorders (BRIAN> 40) [45.4±13.5, 67 (40.0%) female gender].

Patients with circadian rhythm disorders showed significantly higher scores in rating scales evaluating passive (p=<0.001) and active (p=0.002) suicidal ideation, plans for suicide (p=0.012) and depressive symptoms (p=<0.001). They also shower significantly lower score in the rating scale measuring resilience (RSA) (p=0.032**)** and in the subscales of resilience measuring planned future (p=0.015) and structured style (p=0.036) (**table 1)**. They also showed significantly higher scores on the rating scales (DERS total score) (p=0.032) and subscales measuring emotion dysregulation such as non-acceptance of emotion (p=0.003), impulsivity (p=0.037), difficulties in goal-directed behaviors (p=0.004), limited access to effective regulatory strategies (p=0.009), (**table 1**).

b) Correlations among variables

Results of Spearman's correlations for non-normally distributed variables and Pearson's correlations for normally distributed variables are shown in **table 2**. It is evident that depressive symptoms were significantly correlated with chronobiological dis-rythmicity, emotion dysregulation and with low resilience in the capacity to plan future, while manic symptoms were significantly related to emotional impulsivity (see **table 2** for details).

Suicidal risk (SSI total score) was significantly related to depressive symptoms, to all areas of circadian rhythm disturbances, to emotion dysregulation in particular to subscales measuring non acceptance of emotion, impulsivity, difficulties in goal-directed behaviors, limited access to effective regulatory strategies, (**table 2**), to low resilience in the total score and to low resilience in the subscale regarding the ability to plan future.

Additionally, low resilience total score was related to chronobiological dis-rythmicity in the total score and to difficulties in effective regulatory strategies. Low resilience regarding the ability to plan future was related to the chronobiological dis-rythmicity of sleep, social life and eating pattern and to the dysregulation of effective regulatory strategies. Low resilience in structured style was related to the chronobiological dis-rythmicity of sleep and social life, to emotion dysregulation in particular to dysregulation of effective regulatory strategies. Low resilience regarding the perception of self was related to the chronobiological dis-rythmicity of daily life activities. Emotional impulsivity, difficulties engaging in goal-directed behaviors, limited access to effective regulatory strategies, lack of emotional awareness and non-acceptance of emotions were additionally related to chronobiological dis-rythmicity of all areas.

Results of linear regression analyses (**table 3**) showed that circadian rhythm disorders (BRIAN total score >40) predicted depressive symptoms OR 4.00 p=0.001, suicidal risk OR 2.51, p=0.024, emotion dysregulation OR 2.28, p=0.022 and low resilience OR 2.70, p=0.030.

Linear regression analyses showed that significant predictors of depressive symptoms were: chronobiological dis-rythmicity of sleep, social life, daily activities, and eating pattern. They were also related to DERS difficulties in regulatory strategies, lack of emotional awareness and to low resilience regarding the ability to plan future. In the multiple regression model including depressive symptoms as the dependent variable, delayed rhythms of sleep, daily activities, and difficulties in regulatory strategies remained significant (**table 4**).

Linear regression analyses showed that depressive symptoms, chronobiological dis-rythmicity of sleep, social life, daily activities, and eating pattern significant were predictors of passive suicidal ideation. Passive suicidal ideation was also related to DERS difficulties in regulatory strategies, impulsivity and to low resilience regarding the ability to plan future. In the multiple regression model, including passive suicidal ideation as the dependent variable, chronobiological dis-rythmicity of social life and low resilience regarding the ability to plan future remained significant (**table 3**).

Linear regression analyses showed that passive suicidal ideation, depressive symptoms, circadian rhythm disturbances of sleep, social life, daily activities, DERS difficulties in regulatory strategies, impulsivity and to low resilience regarding the capacity to plan future were significant predictors of active suicidal ideation. In the multiple regression model including active suicidal ideation as the dependent variable, passive suicide ideation remained significant (**table 3**).

Linear regression analyses revealed that that passive and active suicidal ideation, depressive symptoms, chronobiological dis-rythmicity of social life, DERS Difficulties in regulatory strategies, impulsivity and to low resilience regarding the capacity to plan future were significant predictors of suicidal plans. In the multiple regression models active suicidal ideation and impulsivity remained significant (**table 3**).

c) Mediation analyses

Results of the mediation analyses for depressive symptoms (BDI total score) highlighted that the low resilience in the ability to plan future (RSA subscale planned future) and emotion dysregulation (DERS total score) acted as mediators between chronobiological dis-rythmicity (BRIAN total) and depressive symptoms

Table 1. *Demographic and psychometric variables*

	Patients with Bipolar Disorder Depressive episode (N°=197)	**Patients with Delayed circadian rhythms BRIAN> 40** (N°=118)	**Patients without Delayed circadian rhythms BRIAN≤40** (N°=79)	**t or χ2** (df=2)	*p*
Age (years) (m±SD)	46.4±13	45.4±13.5	50.1 ± 13.3	0.19	0.052
Gender (female) N°(%)	113 (43.0)	67(4.0)	46(41.4)	0.16	0.435
Living alone N°(%)	44 (22.8)	26(21.1)	18 (25.7)	1.43	0.168
Divorced or not married N°(%)	83(54.2)	48(49.1)	35(62.8)	0.38	0.149
Unemployment N°(%)	25(13.2)	18(15.2)	8(11.4)	0.05	0.321
Illness duration (years) (m±SD)	18.2±11.5	19±11.4	17.9 ± 11.6	0.51	0.605
Bipolar disorder I, II N°(%)	94 (48.9)	56(49.0)	38(40.0)	0.65	0.469
Mixed features N(%)	101(44.1)	68(75.6)	50(29.0)	0.08	0.435
Anxiety comorbidity N(%)	59(27.1)	36 (27.9)	12(25.7)	0.05	0.444
BRIAN tot (m±SD)	49.1±11.2	52.7±7.7	35.3 ±4.5	13.8	**<0.001**
Resilience scale RSA tot (m±SD)	87.3±14.0	86.1±13.7	92.6±15.6	-2.05	**0.032**
Perception of Self -RSA	13.1±4.7	13.5 ±4.7	13.2±4.7	-0.41	0.889
Planned Future -RSA	16.2±8.3	15.5±8.5	20.1±6.9	-2.46	**0.015**
Social Competence- RSA	14.7±6.1	14.6±6.2	14.2±6.4	-0.79	0.937
Structured Style -RSA	13.7±4.9	13.5±3.5	15.3±4.5	-2.11	**0.036**
Family Cohesion- RSA	12.1±3.7	12.1±3.5	11.0±4.2	0.84	0.403
Social Resources -RSA	14.6±6.0	14.5±43.9	15.7±3.2	1.33	0.184
DERS tot (m±SD)	106.1±22.4	107.8±22.8	99.8±19.6	2.03	**0.030**
Non acceptance-DERS	17.7±6.2	18.9±5.9	16.2±5.9	2.92	**0.003**
Impulsivity-DERS	15.5±5.3	16.1±5.1	14.2±4.8	2.15	**0.037**
Difficulties in goal-directed behaviors-DERS	16.1±5.0	16.7±4.6	14.3±4.7	2.95	**0.004**
Difficulties in regulatory strategies-DERS	23.4±6.8	24.1±6.7	20.9±6.5	2.64	0.009
Reduced emotional clarity-DERS	12.9±3.4	12.8±3.4	13.1±3.2	0.44	0.658
Lack of emotional awareness-DERS	21.1±11.2	21.4±12.3	20.8±4.2	0.31	0.752
SSI total (m±SD)	7.2±6.5	7.2±4.5	3.5±4.6	3.72	**<0.001**
Passive suicidal desire	3.1±3.0	3.4±3.8	1.2±2.3	3.13	**0.002**
Active suicidal desire	2.8±3.8	3.1±3.5	1.2±2.3	3.60	**<0.001**
Plans for suicide	0.6±1.2	1.1±1.3	0.34±0.62	2.55	**0.012**
Mood symptom scales					
BDI-II total score (m±SD)	22.2±12.1	24.6±11.5	12.9±07	5.88	**<0.001**
YMRS total score (m±SD)	7.9±6.3	8.6±5.9	7.7±7.2	0.76	0.444
Current drug treatments	N° (%)	N° (%)	N° (%)		
Antidepressants	115(92.3)	73(62.7)	42(50.0)	1.32	0.433
Mood stabilizers	180(92.0)	141(94.2)	39(87.1)	1.92	0.435
Lithium	110(66.9)	70(44.9)	40(37.1)	0.57	0.248
Benzodiazepines	111(57.4)	74(59.3)	40(54.2)	0.03	0.119
Neuroleptics	61(30.8)	36(31.3)	25(30.0)	0.32	0.349

Legend. Demographic and psychometric variables. Description of the total sample of patients with bipolar disorder type I and II depressive episode with and without mixed features and comparison between patients with delayed sleep-wake phase with Biological Rhythms Interview of Assessment in Neuropsychiatry: BRIAN total score ≥40 vs patients without delayed sleep-wake phase BRIAN total score <40. N°=Number, %=percentage, M: mean value, SD: Standard Deviation, t= t test, [a] =χ2:chi square. RSA-Resilience Scale for Adults and RSA subscales Perception of Self, Planned Future, Social Competence, Structured Style, Family Cohesion, Social Resources; DERS: Difficulties in Emotion Regulation Scale and subscales non acceptance of emotion, difficulties engaging in goal-directed behaviors, impulse control difficulties , limited access to effective regulatory strategies, reduced emotional clarity, lack of emotional awareness SSI: Scale for Suicide Ideation; Beck Depression Inventory-II, YMRS: Young Mania Rating Scale. Significance is in bold.

regulatory strategies, difficulties in engaging in goal-directed behaviors with non acceptance of emotions.

Our findings may indicated that circadian rhythm disturbances in sleep, daily-life activities and social life as assessed with the BRIAN, may be related to depressive symptoms, low level of resilience, emotion dysregulation and suicide risk as well.

These findings, especially our mediation analyses, may show that BDs are complex disorders involving the interaction of multiple factors, that may include the role of circadian rhythm alterations as a key factor contributing to the severity of mood symptoms, emotion dysregulation and impaired resilience hence contributing to mood symptoms and suicidal risk.

Table 2. *Correlations among variables in patients with bipolar disorder type I and II*

	SSI tot	BDI-II	YMRS	BRIAN total	BRIAN sleep	BRIAN activity	BRIAN Social	BRIAN eating	DERS tot	DERS Impuls	DERS goal	**DERS** aware	DERS Strategies	DERS Non accept	DERS clarity	RSA tot	RSA Plan. Future	**RSA Struct Style**	RSA Percept of Self
SSI tot	1																		
BDI-II	**0.31** <0.001**	1																	
YMRS	0.10 0.182	0.02 0.651	1																
BRIAN tot	**0.31** <0.001**	**0.51** <0.001**	0.03 0.854	1															
BRIAN sleep	**0.21** 0.005**	**0.37** <0.001**	0.09 0.17	**0.68 <0.001**	1														
BRIAN activity	**0.18* 0.019**	**0.50** <0.001**	0.10 0.155	**0.63** <0.001**	**0.49** <0.001**	1													
BRIAN social	**0.32** <0.001**	**0.29** <0.001**	0.04 0.223	**0.72** <0.001**	**0.23** 0.001**	**0.30** 0.001**	1												
Brian eating	**0.19* 0.010**	**0.31** <0.001**	0.09 0.903	**0.68** <0.001**	**0.35** <0.001**	**0.13* 0.038**	**0.27** <0.001**	1											
DERS tot	**0.15* 0.040**	**0.46** <0.001**	0.07 0.235	**0.35** <0.001**	**0.36** <0.001**	**0.32** <0.001**	**0.36** <0.001**	**0.27** <0.001**	1										
DERS Impuls.	0.27** <0.001	0.29** <0.001	**0.19** 0.006**	**0.37** <0.001**	**0.27** <0.001**	**0.21** 0.002**	**0.25** <0.001**	**0.27** <0.001**	**0.56** <0.001**	1									
DERS goal	0.13 0.072	**0.32** <0.001**	0.002 0.987	**0.38** <0.001**	**0.29** <0.001**	**0.33** <0.001**	**0.29** <0.001**	**0.14* 0.048**	**0.51** <0.001**	**0.50** <0.001**	1								
DERS aware	**-0.20** 0.003**	**-0.18* 0.011**	-0.03 0.223	-0.05 0.485	**-0.15* 0.036**	-0.14 0.051	**-0.15* 0.034**	**-0.17* 0.015**	**-0.28** <0.001**	0.10 0.135	**0.37** <0.001**	1							
DERS strategy	**0.22** 0.003**	**0.48** <0.001**	0.01 0.885	**0.39** <0.001**	**0.37** <0.001**	**0.35** <0.001**	**0.37** <0.001**	**0.26** <0.001**	**0.84** <0.001**	**0.48** <0.001**	**0.47** <0.001**	**-0.29** <0.001**	1						
DERS non accept	0.09 0.216	**0.45** <0.001**	0.015 0.883	**0.29** <0.001**	**0.33 <0.001**	**0.29** <0.001**	**0.33** <0.001**	**0.20** 0.004**	**0.75** <0.001**	**0.29** <0.001**	**0.63** <0.001**	0.04 0.502	**0.60** <0.001**	1					
DERS clarity	0.04 0.678	0.15* 0.036	0.08 0.228	0.08 0.236	0.04 0.542	0.04 0.548	0.04 0.560	**0.16* 0.021**	**0.51** <0.001**	**0.21** 0.002**	0.22 0.728	**-0.32** <0.001**	**0.36** <0.001**	**0.18** 0.009**	1				
RSA tot	**-0.22** 0.009**	-0.10 0.170	-0.03 0.721	**-0.21** 0.008**	-0.15 0.061	0.004 0.963	-0.15 0.061	-0.12 0.112	0.11 0.417	-0.05 0.481	-0.11 0.152	-0.06 0.233	**0.13* 0.011**	0.03 0.700	0.01 0.259	1			
RSA plann. future	**-0.29** 0.002**	**-0.18* 0.037**	0.09 0.295	-0.27** 0.001	-0.17* 0.040	-0.096 0.269	**-0.16* 0.045**	**-0.27** 0.001**	0.02 0.795	-0.03 0.566	-0.10 0.102	-0.04 0.621	**-0.20** 0.016**	0.19 0.823	0.05 0.540	**0.60** <0.001**	1		
RSA struct. style	-0.07 0.546	-0.09 0.876	0.01 0.324	**0.19** 0.021**	**0.16* 0.042**	-0.042 0.617	0.08 0.301	**-0.17* 0.035**	**0.16* 0.045**	0.07 0.403	0.16 0.865	-0.13 0.110	**-0.20** 0.006**	0.10 0.876	0.07 0.402	**0.63** <0.001**	**0.41** <0.001**	1	
RSA percept of self	0.19 0.232	-0.02 0.574	0.01 0.229	0.08 0.289	0.07 0.375	**-0.17* 0.038**	-0.08 0.290	0.10 0.453	0.09 0.233	0.003 0.987	0.17 0.840	-0.06 0.548	0.04 0.588	0.05 0.511	0.04 0.573	**0.43** <0.001**	0.03 0.675	**0.18* 0.025**	1

Coefficients of Spearman's correlation for non-normally distributed variables and Pearson's correlation for normally distributed variables.SSI: Scale for Suicide Ideation, RSA-Resilience Scale for Adults, RSA subscales Planned Future, Structured Style, Perception of Self. BRIAN Biological Rhythms Interview of Assessment in Neuropsychiatry: BRIAN total and subscales, Sleep, Activities, Social life, DERS: Difficulties in Emotion Regulation Scale and subscales non acceptance of emotion, difficulties engaging in goal-directed behaviors, impulse control difficulties, limited access to effective regulatory strategies, reduced emotional clarity, lack of emotional awareness BDI-II: Beck Depression Inventory-II, YMRS: Young Mania Rating Scale. Significance is in bold.*=p<0.05, **=p<0.001.

Table 3. *Linear and multiple regression analyses on depressive symptoms, and passive, active ideation and preparatory behaviors in patients with bipolar disorder type I and II*

Logistic regression	Depressive symptoms-BDI O.R.	C.I.- 95%	p	Suicidal Risk-SSI O.R.	C.I.- 95%	p	Emotion dysregulation-DERS O.R.	C.I.- 95%	p	Low resilience-RSA O.R.	C.I.- 95%	p
Circadian rhythm disturbances BRIAN tot >40	4.00	1.774-9.019	**0.001**	2.51	1.129-5610	**0.024**	2.28	1.124-4.653	**0.022**	2.70	1.090-6.670	**0.030**

Depressive symptoms	Univariate B (SE)	p	Multivariate B (SE)	**p**
BRIAN Sleep	**1.2 (0.22)**	**<0.001**	**0.61 (0.26)**	**0.025**
BRIAN Social	**1.2(0.28)**	**<0.001**	0.34 (0.28)	0.230
BRIAN Activity	**1.5 (0.19)**	**<0.001**	**0.74 (0.22)**	**0.011**
BRIAN Eating	**1.2 (0.26)**	**<0.001**	0.10 (0.29)	0.211
DERS Difficulties in regulatory strategies	**0.85 (0.11)**	**<0.001**	**0.48 (0.14)**	**0.001**
DERS Lack of emotional awareness	**0.20 (0.08)**	**0.011**	0.10(0.10)	0.234
RSA Planned Future	**-0.36 (0.17)**	**0.037**	-0.23 (0.15)	0.144
Passive suicidal ideation-SSI	Univariate B (SE)	p	Multivariate B (SE)	**p**
BRIAN Sleep	**0.20 (0.06)**	**0.001**	0.13 (0.08)	0.675
BRIAN Social	**0.30 (0.07)**	**<0.001**	**0.19 (0.09)**	**0.046**
BRIAN Activity	**0.13 (0.05)**	**0.021**	0.01 (0.07)	0.827
BRIAN Eating	**0.17 (0.07)**	**0.002**	0.04 (0.09)	0.432
DERS Difficulties in regulatory strategies	**0.4 (0.04)**	**0.002**	0.07 (0.05)	0.225
DERS Impulsivity	**0.9(0.03)**	**0.010**	0.01 (0.04)	0.289
RSA Planned Future	**-0.15 (0.04)**	**0.002**	**-0.11 (0.04)**	**0.026**
BDI	**0.07 (0.01)**	**<0.001**	0.04 (0.02)	0.120
Active suicidal ideation-SSI	Univariate B (SE)	p	Multivariate B (SE)	p
Passive suicidal ideation	**0.96 (0.62)**	**<0.001**	**0.91 (0.06)**	**<0.001**
BRIAN Sleep	**0.20 (0.06)**	**0.001**	0.05(0.06)	0.675
BRIAN Social	**0.30 (0.07)**	**<0.001**	0.06 (0.03)	0.352
BRIAN Activity	**0.13 (0.05)**	**0.021**	0.04 (0.06)	0.432
DERS Difficulties in regulatory strategies	**0.4 (0.04)**	**0.002**	0.07 (0.05)	0.225
DERS Impulsivity	**0.9(0.03)**	**0.010**	0.01 (0.04)	0.289
RSA Planned Future	**-0.15 (0.04)**	**0.002**	-0.01 (0.03)	0.728
BDI	**0.07 (0.01)**	**<0.001**	0.03 (0.02)	0.099
Preparatory behaviors -SSI	Univariate B (SE)	p	Multivariate B (SE)	**p**
Active suicidal ideation	**0.16 (0.01)**	**<0.001**	**0.15(0.05)**	**0.004**
Passive suicidal ideation	**0.21 (0.08)**	**<0.001**	0.02(0.06)	0.236
BRIAN Social	**0.10 (0.03)**	**0.002**	0.02 (0.02)	0.204
DERS Difficulties in regulatory strategies	**0.4 (0.04)**	**0.002**	0.006 (0.04)	0.478
DERS Impulsivity	**0.4(0.01)**	**0.003**	**0.03 (0.01)**	**0.048**
RSA Planned Future	**-0.05 (0.02)**	**0.027**	-0.001 (0.01)	0.966
BDI	**0.01 (0.008)**	**0.038**	0.009(0.08)	0.435

Legend: **Linear and multiple regression analyses on depressive symptoms, passive, active suicidal ideation and suicidal preparatory behaviors in patients with bipolar disorder type I and II .** Results of linear and multiple and logistic regression analyses among depressive symptoms Back Depression Inventory-BDI, Passive suicidal ideation, active suicidal ideation, Preparatory behaviors -SSI Scale for Suicide Ideation and other variables in patients with bipolar disorder type I and II, depressive episode. SSI: Scale for Suicide Ideation, RSA-Resilience Scale for Adults RSA subscale Planned Future. BRIAN Biological Rhythms Interview of Assessment in Neuropsychiatry: BRIAN subscales, Sleep, Activities, Social life, DERS: Difficulties in Emotion Regulation Scale and subscales non acceptance of emotion, difficulties engaging in goal-directed behaviors, impulse control difficulties, limited access to effective regulatory strategies, reduced emotional clarity, lack of emotional awareness, BDI-II: Beck Depression Inventory-II, YMRS: Young Mania Rating Scale. B= unstandardized regression coefficient. S.E.: Standard Error, OR: Odd Ratio. Significance is in bold.

(**figure 1**) (Z= 3.85, SE: 0.034, p=0.0001). In addition, DERS difficulties in regulatory strategies acted as a mediator in the association between dis-rythmicity of sleep (BRIAN Sleep) and daily life activities (BRIAN Activity) and depressive symptoms (Z= 4.36, p=0.0001, Z= 3.88, SE: 0.034, p=0.0001) (**figure 1**).

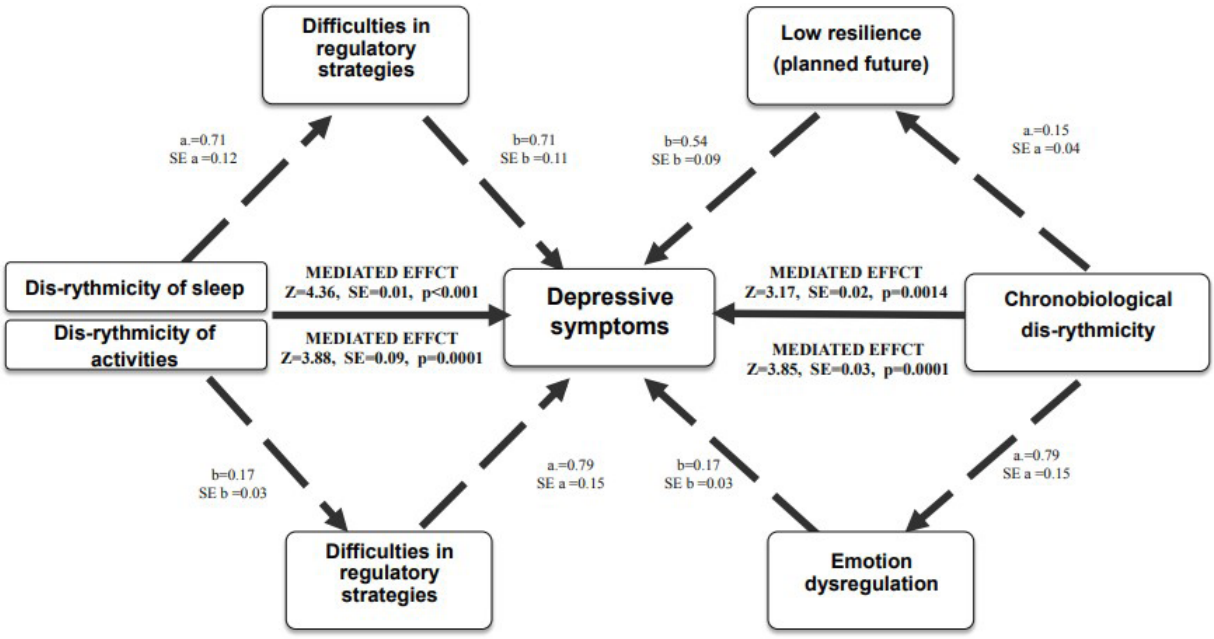
For suicidal risk (SSI total score), the low resilience in the capacity to plan future (RSA subscale planned future) and emotion dysregulation (DERS total score) acted as mediators between chronobiological dis-rythmicity (BRIAN total) and suicidal risk (Z=2.00, SE: 0.008, p=0.045, Z= 3.28, SE: 0.050, p=0.001) (**figure 2**), DERS impulsivity between dis-rythmicity of social life (BRIAN Social) and suicidal risk (Z=2.14, p=0.032) (**figure 2**). Emotion dysregulation in the total score, emotional impulsivity and chronobiological dis-rythmicity acted as mediators between depressive symptoms (BDI total) and suicidal risk (Z= 3.90, p=0.0009, Z= 3.02, p=0.002, Z= 2.29, p=0.021) (**figure 3**). No other mediations resulted significant.

Within this framework, these data suggest possibly useful to inform preventive strategies by acting on the dysregulation of sleep and circadian rhythms with available chronotherapeutics (Gottlieb et al., 2019).

In this study, we were able to show that the majority of BD individuals may hold circadian rhythm disturbances, mostly delayed sleep phase syndrome as assessed with the BRIAN, and showed a greater severity not only of depressive symptoms, but also of suicidal ideation and plans. Bipolar individuals with circadian rhythm disturbances of sleep, social life and daily-life activities and of eating pattern showed lower levels of resilience. In particular, their resources of resilience resulted impaired especially in bipolar subjects with circadian rhythm disturbances, regarding those areas involved in the ability to plan future, to plan ahead, formulate clear goals, and to organize own time, goal and routine oriented ability. No differences were found among gender and type of bipolar disorder

These findings might be considered in line with those showing that evening chronotype may be related

Figure 1.

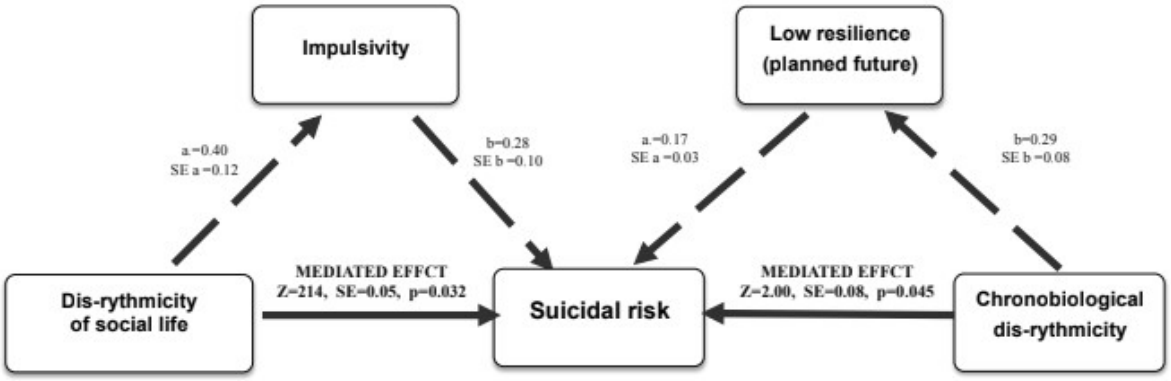


Results of mediation analyses. Low resilience in the ability to plan future (concerning the positive outlook on one's own future, sense of belief about the opportunity to succeed and the ability to plan ahead and formulate clear goals) acted as a mediator between circadian rhythm disturbances and depressive symptoms; similarly emotion dysregulation acted as a mediator between circadian rhythm disturbances and depressive symptoms. Difficulties in effective regulatory strategies acted as a mediator between circadian sleep and daily life activities rhythm disturbances and depressive symptoms

Discussion

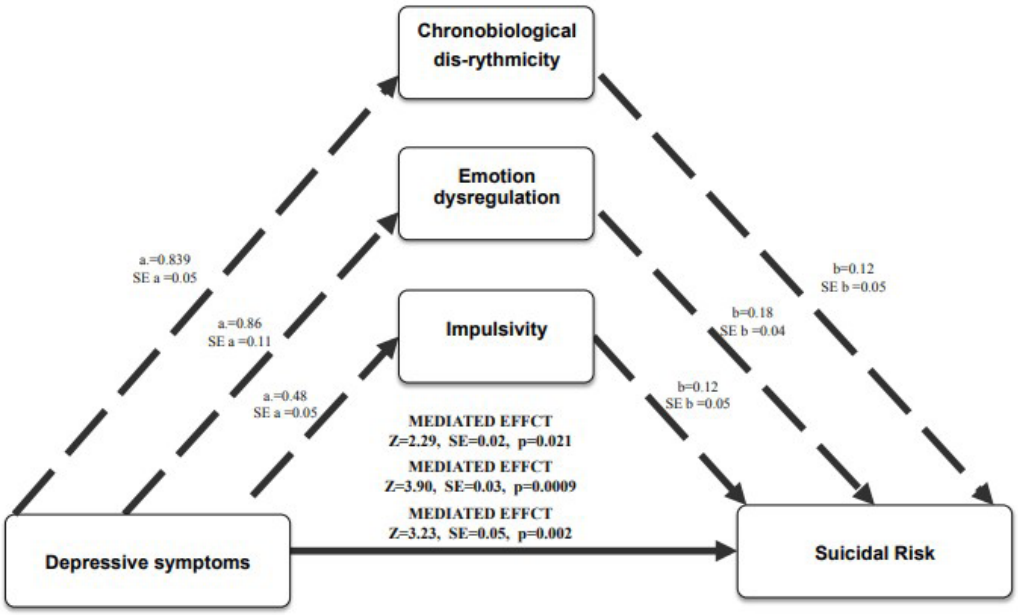
The results of the present study showed that patients suffering from BDs with circadian rhythm disturbances hold not only a greater severity of depressive symptoms, suicidal ideation and plans, but also lower levels of resilience in particular concerning the ability in planning future, in goal, routine oriented ability. In particular those subjects with circadian rhythm disturbances characterized by delayed phases, also experienced more difficulties in regulating emotions showing greater impulsivity, limited access to effective to low resilience in non clinical population (Murray et al., 2020) and in bipolar individuals (Chung et al., 2018), and with the hypotheses showing a pivotal role of circadian desynchronization in compromising allostatic responses, enabling organisms adapt to environmental challenge, by disrupting the stress axis (Rao & Androulakis, 2019; Kinlein & Karatsoreos, 2020). In particular, circadian sleep alterations have been considered as stressors since they directly alter catecholamine and cortisol release and may lead to stress system overload (McEwen & Karatsoreos, 2015).

Figure 2.



Results of mediation analyses. Impulsivity acted as a mediator between circadian social rhythm disturbances and suicidal risk, low resilience in the ability to plan future and emotion dysregulation acted as mediators between circadian rhythm disturbances and suicidal risk

Figure 3.



Results of mediation analyses. Impulsivity, emotion dyregulation and circadian rhythm disturbances acted as mediators between depressive symptoms and suicidal risk

It is tempting to hypothesize that circadian rhythm alterations in mood disorders may affect the stress-vulnerability/resilience circuitry hence impairing the individual resources of resilience. In this framework, it could be possible that by affecting resilience circadian rhythm alterations might contribute to mood symptoms and suicidal risk in BD.

Interestingly, one of the main objective of behavioral chronotherapeutic approaches regards organizing own time and goals and potentiating the routine oriented ability in order to maintain synchronized rhythms and prevent relapse and recurrence in BD (Frank et al., 2006). We would suggest that by targeting circadian rhythm alterations with chronotherapeutics might provoke a great impact on stress vulnerability/resilience dimension enhancing resilience in BDs.

Bipolar individuals with circadian rhythm disturbances showed greater problems with emotion regulation in particular holding greater impulsivity, limited access to effective regulatory strategies, difficulties in engaging in goal-directed behaviors and non-acceptance of emotions. These findings are in agreement with previous data collected separately in different studies showing emotional dysregulation in BD II with circadian rhythm alterations, emotional impulsivity in individuals displayed phase-delayed patterns of sleep (McGowan & Coogan, 2018), increased reward sensitivity, impulsivity and likelihood of engaging in risky behaviors in relation with circadian misalignment in adolescents (Logan et al., 2018).

Recent theories (Vadnie et al., 2017; Geoffroy, 2018; *Wirz-Justice & Benedetti, 2020)* hypothesized that *chonobiological dis-rhythmicity* might 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. In particular, the key role of sleep in regulating stress system and emotions has been

hypothesized (Walker, 2009; Lo Martire et al., 2020), while circadian sleep disturbances have been related *to low resilience and emotion dysregulation.*

In our BD individuals during acute depressive episodes, correlations and regression analyses revealed that circadian rhythm disturbances, in particular the dis-rhythmicity of sleep and daily life activities, emotion dysregulation, and impaired resilience in the ability to plan future were strongly related to depressive symptoms while emotional impulsivity contributed to manic symptoms. These findings may extend previous works in which circadian rhythm disturbances, resilience and emotion regulation, were studied separately in BDs and other psychiatric disorders (Roy et al., 2007; Townsend & Altshuler, 2012; Choi et al., 2015; Lee et al., 2017; Angeler et al., 2018; Deng et al., 2018; Logan et al., 2018; McGowan & Coogan, 2018; Mizuno et al., 2018; Palagini et al., 2019; Post et al., 2018; Murray et al., 2020; Nunes & da Rocha, 2022). By contrast, we evaluated all these factors in the same sample, while revealing a complex interplay among circadian rhythm disturbances, impaired resilience, emotions dysregulation and mood symptoms. In particular, delayed circadian rhythms of sleep, daily life activities, social life, difficulties in emotional regulatory strategies, lack of emotional awareness and impaired resilience in planned future were interrelated and collectively contributed to depressive symptoms, hence confirming BDs as complex disorders involving the possible interaction of multiple factors.

The correlations and regression analyses revealed that circadian rhythm disturbances in the total score, emotional impulsivity, lack of emotional awareness, impaired resilience in the total score, in the ability to plan future and in the perception of self concerning the confidence in own abilities, self-confidence and self-efficacy were interrelated and collectively contributed to the suicidal risk in BDs. In particular, alterations in rhythms of sleep and social life were interrelated with emotional impulsivity, lack of emotional awareness impaired resilience in the ability to plan future, to formulate clear goals, and to organize own time collectively contributing to suicidal risk. Interestingly, circadian rhythm alteration of sleep was specifically related to alterations in resilience regarding self-confidence and self-efficacy contributing to suicidal risk, and circadian rhythm alteration of sleep, social life and activities were related to low resilience in structured style. It is possible that circadian rhythm dysregulation would affect different aspects of individual resources contributing to the resilience.

In our opinion, the present findings integrate previous works in which circadian rhythm disturbances, resilience and emotion regulation, were studied separately in relation to suicidal risk in BDs. By contrast, we revealed that complex interplays among circadian rhythm disturbances of sleep and social life, impaired individual sources of resilience and emotional impulsivity were interrelated and collectively contributed to the suicidal risk in BD.

Results of the mediation analyses may shed some lights about this complex interplay and showed that chronobiological dis-rythmicity may hold a direct and indirect effect on depressive symptoms by affecting resilience and emotion regulation. In particular dis-rythmicity of sleep and daily life activities showed a direct and an indirect effect on depressive symptoms by affecting the access of effective emotional regulatory strategies (**figure 1**).

For suicidal risk (SSI total score) chronobiological dis-rythmicity showed a direct and indirect action by favoring low resilience in the capacity to plan future and emotion dysregulation. In particular chronobiological dis-rythmicity of social life also showed an indirect effect by favoring emotional impulsivity

These findings may be considered in line with the hypothesis that *chonobiological dis-rhythmicity* might contribute to mood disorders and suicidal risk by dysregulating most of the systems involved in mood, stress system and emotion regulation (Vadnie & McClung, 2017; Geoffroy, 2018; *Wirz-Justice & Benedetti, 2020*) and with the key role of sleep in regulating stress system and emotional regulation. Since circadian sleep alterations have been hypothesized to affect cognition (Watherhouse, 2010), our hypothesis is that alterations of sleep process might also affect cognitive components of resilience regarding planning future and organizing day life activities, or self efficacy and of emotion regulation, by favoring emotional impulsivity and difficulties in regulatory strategies. Disturbed sleep may lead to greater impulsive action alternatively or additionally maladaptive goal-directed behavior and social rhythm instability may lead to later bedtimes and irregular circadian entrainment and may contribute to impulsive behaviors in BD (McGowan et al., 2020).

Taken together, the findings of the present study emphasize the need to assess circadian rhythm dysregulation in the clinical practice of BD. We call for implementing it in the routine clinical evaluation of bipolar patients, together with the evaluation of emotion regulation and resilience. A better screening of these dimensions might provide additional preventive strategies and/or improve treatments that should include chronotherapeutics in the clinical practice. Since by enhancing stress resilience in at-risk populations may prevent the onset of stress-induced psychopathology (Faye et al., 2018), by targeting circadian rhythm disturbances might potentially modify the clinical features of BD improving resilience and regulating emotions.

Limitations

These results should be interpreted in light of several limitations including the cross-sectional design preventing any causal interpretations. Consequently, longitudinal studies are needed to confirm causal relationships, but also warrant larger samples of patients and other types of mood disorders including psychotic symptoms, anxiety or other features of BD. It could be also interesting to examine patients who attempted suicide to better examine the direction of risk and be able to generalize these findings.

Objective measures of circadian rhymes activity and of stress system should be included in future studies in BDs (Zhou et al., 2021). Also, BRIAN continuos parameters and sensitivity for dectecting other circadian sleep disturbances shoul be evaluated in future studies.

Conclusions

In conclusion, our study suggests that: i) bipolar patients during a major depressive episode with circadian rhythm disturbances may hold a greater severity not only of depressive symptoms and suicidal ideation and plans, but also of low resilience and emotion dysregulation; ii) circadian rhythm alterations may be direcly related to depressive symptoms, suicidal ideation and plans iii) circadian rhythm alterations may also be related to low resilience and impulsivity,

via these pathways they may be associated with mood symptoms and suicidal risk ; and iv) circadian alterations of sleep and social life may be related to dyregulations in personal resource of resilience and to dysregulation in regulatory strategies of emotions.

These findings may have clinical implications for systematic screening of circadian rhythms disorders, for a better characterization of BDs, but also for prevention and early intervention strategies with appropriate chronotherapeutic strategies. In particular, treating circadian rhythms disturbances may potentially improve the clinical features of BDs by enhancing resilience and regulating emotion.

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