

Insomnia symptoms predict emotional dysregulation, impulsivity and suicidality in depressive bipolar II patients with mixed features

Laura Palagini ^{*}, Giada Cipollone, Isabella Masci, Danila Caruso, Francescoluigi Paolilli, Giulio Perugi, Dieter Riemann ¹

Department of Clinical and Experimental Medicine, Psychiatric Section, University of Pisa, Azienda Ospedaliera Universitaria Pisana (AOUP), Pisa, Italy

ARTICLE INFO

Available online xxxx

ABSTRACT

Introduction: Insomnia symptoms are very common in Bipolar Disorder. Our aim was to assess the potential association between insomnia, emotion dysregulation and suicidality in subjects with Bipolar Disorder.

Methods: Seventy-seven subjects with Bipolar Disorder type II with a depressive episode with mixed features were recruited. Patients were assessed with SCID-DSM-5, the Insomnia Severity Index (ISI), the Difficulties in Emotion Regulation Scale (DERS), the Scale for Suicide Ideation (SSI) while evaluating manic and depressive symptoms.

Results: Subjects with insomnia symptoms compared to those without showed higher scores in the DERS scale and subscales, including impulsivity, and in the SSI scale. Insomnia symptoms significantly predicted the severity of depressive symptoms, emotion dysregulation, and suicidality in subjects with bipolar disorder. In particular, insomnia was related to difficulties in some areas of emotion regulation including impulsivity. Emotion dysregulation significantly mediated the association between insomnia and depressive symptoms ($Z = 2.9, p = 0.004$). Furthermore, emotional impulsivity mediated the association between insomnia symptoms and suicidality ($Z = 2.2, p = 0.03$).

Conclusion: In our study, subjects with bipolar disorder suffering from insomnia experienced a greater severity of depressive symptoms and suicidality compared to subjects without insomnia. Insomnia was associated with emotion dysregulation, impulsivity and suicidality. Further research is necessary to investigate if these latter features may benefit from early insomnia treatment in subjects with bipolar disorder.

© 2018 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Mood disorders includes a spectrum of conditions that can encompass elevated mood such as mania/hypomania and depressed mood [1]; major forms, such as major depressive unipolar and bipolar disorders, are, among all, the most prevalent and likely to be recurrent, chronic and disabling [2,3]. Therefore the impact on public health is a matter of major concern leading to global burdens of disease in terms of disability, morbidity, premature mortality [2,4,5] and to a significant risk for suicidality [3,6]. 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 improving treatment strategies.

Insomnia is a clinically significant feature of bipolar disorder, listed as a diagnostic criterion for mood disorders according to the Diagnostic and Statistical Manual of Mental Disorders-DSM, starting as early as 1980 [7]. It is highly prevalent across the entire course of bipolar disorder, with 80–100% of individuals experiencing it during a depressive episode, 30–35% during a manic and mixed episode and 45–55% in the inter-episodic phase [8–11]. Insomnia was related to bipolar disorder severity [9] and to emotional hyper-reactivity during remitted phases [12,13]. Insomnia was shown to increase the risk of bipolar disorder relapse and recurrence as it is one of the most frequent residual symptoms [13]; it is also an independent risk factor for bipolar disorder and a frequent early sign occurring prior to both depressive and manic episodes [14–16]. Recently, it has been shown that targeting insomnia may favorably impact on the trajectory of bipolar disorders [10,17]. Although insomnia might be a potentially-modifiable early marker associated with emotion dysregulation, impulsive behaviors and suicidality in a variety of psychiatric disorders [18–20] its potential association with these clinical features in bipolar disorder is to date poorly understood.

Namely, emotion dysregulation has been proposed as a critical component in the development and maintenance of mood disorders with a

^{*} Corresponding author at: Psychiatric Clinic, Department of Clinical and Experimental Medicine, University of Pisa, Via Roma 67, 56100 Pisa, Italy.

E-mail address: lpalagini@tiscali.it (L. Palagini).

¹ Department of Clinical Psychology and Psychophysiology/ Sleep Medicine, Center for Mental Disorders, University of Freiburg, Freiburg, Germany.

feedback recursively and dynamic loop reinforcing mood instability [21–23]. Emotion dysregulation is defined as an impairment in the modulation of some aspects of emotional functioning including 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 [21–23]. Although emotional dysregulation has been related to mood instability, impulsive behaviors, and increased risk of suicidality in individuals with bipolar disorder [21–23], its association with insomnia during acute phases of bipolar disorder remains unclear.

As already suggested, insomnia could contribute to emotional dysregulation, consequently leading to exaggerated neural and behavioral reactivity to experiences [24,25]. In fact, a dysfunction in the neural circuitry underlying emotion regulation was observed in individuals suffering from insomnia (for an overview see [26]). Sleep disruption, including insomnia, is shown to affect brain regions deputized to emotion, motivation and cognition regulation, thus, by impairing the top-down modulation of emotional processing, contributing to emotional dysregulation [27,28]. In addition, insomnia was found to be related, via negative effect on prefrontal cortical functioning, to impairments in both basic cognitive functions and higher-order cognitive processing involved in supervisory control, problem solving, flexibility and self-control [29,30].

Therefore, insomnia is associated to the alteration of the entire decision-making process leading to risky decisions, impulsive and aggressive behaviors [19,31].

Insomnia can be identified as an independent risk factor for suicide [32]. Different mechanisms have been hypothesized to underline this association. Hypothesis were made that insomnia-related emotion dysregulation and the impairment of decision-making processes related to insomnia may lead to impulsive and aggressive behaviors: these alterations may increase the risk of suicidality in relation to insomnia (for an overview see [20,32]). Although insomnia have been related to emotional dysregulation, impulsive behaviors, and increased risk of suicidality [18,21–23], their association during acute phases of bipolar disorder is still unclear.

In consideration of the above mentioned hypotheses about the role of insomnia in emotion dysregulation, impulsive behaviors and suicidality, the focus of our research was to investigate their potential relationship in a sample of mixed depressive patients with bipolar disorder type II. We hypothesized that insomnia symptoms may play a role in emotion dysregulation, impulsive behaviors and suicidality during acute phases of bipolar disorder. We also aimed to explore the potential processes underlying the relationship between these variables by using a mediation analyses. Since emotion dysregulation and impulsivity may play a potential role linking insomnia to suicidality, we investigated a possible mediation role for emotional dysregulation/impulsivity in subjects with bipolar disorder.

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 characterize insomnia in different types of mood disorders. The subjects in our sample were diagnosed with Bipolar Disorder type II during a major depressive episode with mixed features, satisfying the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria [1], 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 of insomnia in other forms of mood disorders will be evaluated and compared.

Our inclusion criteria were 1) a current diagnosis of major depressive episode with mixed features in Bipolar Disorder type II 2) age between 18 and 65 years and 3) the willingness to sign an informed

consent to the study and were hospitalized at the Psychiatry Unit of the University of Pisa, Italy. All subjects were assessed using standardized questionnaires, including the structured interview for DSM-5 (Structured Clinical Interview for Axis I Disorders- SCID-I) [33] investigating the presence of a current or lifetime psychiatric diagnosis, the Insomnia Severity Index [34] rating insomnia symptoms, the Difficulties in Emotion Regulation Scale (DERS) [35,36] evaluating emotion dysregulation and Scale for Suicide Ideation (SSI) measuring suicidality [37]. The Beck Depression Inventory- II (BDI-II) [38] and the Young Mania Rating Scale (YMRS) [39] were used to evaluate respectively depressive and manic symptoms. Sleep disorders were assessed through a clinical evaluation conducted by an expert in sleep medicine (LP) and the use of other sleep questionnaires [40] to rule out other sleep disorders (i.e. obstructive sleep apnea syndrome, restless legs syndrome, circadian sleep disorders etc.). All the subjects also filled clinical report forms which included current pharmacological therapy, at baseline.

The exclusion criteria were: 1) a current and lifetime diagnosis of substance abuse, 2) a depressive episode with psychotic features, 3) other types of bipolar disorder, 4) a cognitive impairment (Mini Mental State Evaluation [41]), 5) a current diagnosis of sleep disorders other than insomnia.

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 [1] was performed using the Structured Clinical Interview for Axis I Disorders (SCID-5) [33]. 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. Insomnia severity

Insomnia severity was evaluated with the Insomnia Severity Index (ISI) [34]. The Index is a 7-item self-report questionnaire with a two weeks recall period. The total score ranges from 0 to 28. For the purposes of this study, according to the ISI authors' recommendations, an ISI score of ≥ 8 indicated insomnia symptoms. The ISI has been validated in a previous Italian sample [42].

2.1.3. Emotion regulation

Emotion regulation was measured with the Difficulties in Emotion Regulation Scale (DERS) [35]. The DERS is a 36-items and a 5-point scale (ranging from 1 – almost never to 5 – almost always). The total DERS score ranges 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. [36].

2.1.4. Psychiatric scales

Depressive symptoms were assessed using the Beck Depression Inventory (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 to 63. According to the authors' recommendations, a BDI score > 13 is indicative of depressive

Table 1
Demographic and psychometric variables.

	Subjects with bipolar disorder with insomnia (n = 54)	Subjects with bipolar disorder with no insomnia (n = 23)	p
Age (years)	47.6 ± 12	50.3 ± 13	0.371
Gender (female) n°(%)	35 (62.3)	10 (63.8)	0.494
Illness duration (years)	18.2 ± 12.6	20.4 ± 11.6	0.483
Positive family history n°(%)	41(77.6)	18(77.6)	0.818
ISI-insomnia symptoms	12.9 ± 4.9	3.2 ± 1.9	<0.001
DERS total emotion dysregulation	111.1 ± 19.3	94.6 ± 18.1	0.001
DERS non acceptance	19.8 ± 5.8	14.1 ± 5.7	0.001
DERS difficulties in goals-behaviors	17.5 ± 4.3	14.2 ± 4.3	0.017
DERS emotional impulsivity	15.9 ± 4.9	12.4 ± 3.8	0.003
DERS difficulties regulatory strategies	25.1 ± 6	19.1 ± 6.5	0.001
DERS reduced emotional clarity	13.3 ± 2.8	13.3 ± 52.9	0.278
DERS lack of emotional awareness	19.7 ± 6.3	21.3 ± 3.5	0.797
BDI-II-depressive symptoms	23.3 ± 11	16.7 ± 8.2	0.014
YMRS-manic symptoms	8.2 ± 5.3	9.2 ± 6.2	0.505
SSI- suicidality	7.2 ± 5.5	3.7 ± 3.7	0.032
Current drug treatments	N° (%)	N° (%)	
Antidepressants	12(56.8)	28(56.8)	0.595
Mood stabilizers	40(55.8)	12(55.8)	0.102
Lithium	34(64.9)	11(64.9)	0.434
Benzodiazepines	27(56.8)	10(56.8)	0.725
Antipsychotics	35(77)	14(77)	0.944
Anxiety comorbidity	14(17.2)	7(17.2)	0.556

Legend. Data are reported as mean ± standard deviation-SD and percentage. ISI: Insomnia Severity Index, DERS:Difficulties in Emotion Regulation Scale, DERS subscales: DERS Non Acceptance of emotion, DERS Difficulties in goals-behaviors, DERS impulsivity, DERS Difficulties regulatory strategies, DERS Reduced emotional clarity, DERS Lack of emotional awareness. BDI-II: Beck Depression Inventory, YMRS:Young Mania Rating Scale, SSI: Scale for Suicide Ideation. Significance in bold.

symptoms, while moderate/severe depression is indicated by a score of BDI > 20 [38,43]. In this study we used an adjusted total BDI-II score which did not included the item 16 (i.e., changes in sleep) to avoid collinearity with the ISI score.

Manic symptoms were investigated with the Young Mania Rating Scale (YMRS). This is an instrument to be completed by the clinician while conducting the interview on the patient. It is an 11-item scale. Clinicians rate 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 [39,44].

Suicidality was evaluated using the Scale for Suicide Ideation (SSI) [37]. It consists of 19 items assessing 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 total score ranges from 0 to 38 with the higher the total score related to 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 [37,45].

2.2. Statistical analyses

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 with insomnia symptoms (ISI ≥ 8) versus subjects with bipolar disorder without insomnia symptoms (ISI < 8) 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. An a priori power estimation analysis provided a sample size of *n* = 35 with a power of 0.8. Univariate linear and logistic regression analyses were performed in order to test correlations between insomnia symptoms, emotion dysregulation and suicidality in a group of subjects with bipolar disorder while taking into account

other factors (manic/depressive symptoms, current psychiatric comorbidity, current pharmacological treatments, family history for psychiatric disorders, illness duration).

Multiple linear regression models were then built with emotion dysregulation and suicidality as dependent variables. In the case of a significant correlation (*p* < 0.05) between the values and dependent variables on the univariate analyses, the values were used as independent variables. All the multiple regression models were checked for multicollinearity. A variable was excluded from the model if it had a variance inflation factor >10 and a condition number >100 in the Eigenvalues of Centered Correlations. A mediation analysis using the Sobel test [46] was performed in order to study the potential processes that may underling the relationship between these variables. All pathways of the mediation were tested.

3. Results

3.1. Descriptive statistics and comparative analyses

Of the 130 potential participants evaluated, 77 subjects (*n*°48, 62.3% females, mean age 48.4 ± 12.4 years) met the inclusion/exclusion criteria for Bipolar Disorder type II depressive episode with mixed features. Twenty-eight subjects who also suffered from other mental and sleep disorders and 25 subjects who did not complete the evaluations were lastly excluded from the final sample. The comparison between subjects with bipolar disorder with and without insomnia symptoms showed that subjects with insomnia scored higher in the rating scales measuring depressive symptoms and suicidality, and in emotion regulation. In particular, patients in our sample suffering from insomnia were more likely to experience higher difficulties in impulse control, in the access to effective regulatory strategies, in acceptance of emotion and in engaging in goal-directed behaviors (Table 1).

3.2. Correlations between variables

3.2.1. Determinants of emotion dysregulation

We used a univariate analysis in bipolar patients to find a statistically significant positive correlation between emotion dysregulation and both insomnia and depressive symptoms (Table 2). No correlations were observed with other variables considered (illness duration *p*

Table 2
Univariate and multivariate regression analyses on emotion dysregulation in subjects with bipolar disorder.

	Univariate		Multivariate	
	B	p	B	p
DERS				
ISI	1.12	0.002	0.76	0.018
BDI-II	0.96	<0.001	0.86	<0.001
YMRS	0.01	0.092	–	–
DERS non acceptance				
ISI	0.47	<0.001	0.35	<0.001
BDI-II	0.31	<0.001	0.26	<0.001
YMRS	0.04	0.723	–	–
DERS difficulties in goals-behaviors				
ISI	0.19	0.011	0.11	0.131
BDI-II	0.18	<0.001	0.17	<0.001
YMRS	0.04	0.588	–	–
DERS impulsivity				
ISI	0.16	0.044	0.082	0.323
BDI-II	0.17	<0.001	0.171	<0.001
YMRS	0.14	0.013	0.142	0.092
DERS difficulties regulatory strategies				
ISI	0.41	0.001	0.27	0.001
BDI-II	0.35	<0.001	0.31	<0.001
YMRS	0.05	0.668	–	–

Legend: Results of the univariate and multivariate regression analyses between the DERS: Difficulties in Emotion Regulation Scale and DERS subscales: DERS Non Acceptance of emotion, DERS Difficulties in goals-behaviors, DERS impulsivity, DERS Difficulties regulatory strategies and other variables. ISI: Insomnia Severity Index, BDI-II: Beck Depression Inventory, YMRS: Young Mania Rating Scale and other variables. B = unstandardized regression coefficient. Significance in bold.

= 0.72, positive family history for psychiatric illness p = 0.73, benzodiazepines: p = 0.75, antidepressants: p = 0.86, neuroleptics: p = 0.99, lithium: p = 0.17, mood stabilizers: p = 0.78, anxiety comorbidity p = 0.36).

The multiple-regression model including emotion dysregulation as the dependent variable, depressive and insomnia symptoms as independent variables, was found significant (F = 7.2, p ≤ 0.001). Both variables remained related to emotion dysregulation. (Table 2).

DERS subscales such as non-acceptance of emotion, difficulties engaging in goal-directed behaviors, emotional impulsivity and difficulties in regulatory strategies were all significantly related to insomnia symptoms (Table 2).

No correlations were found between these DERS subscales and other variables considered.

3.2.2. Determinants of suicidality

The univariate analysis in subjects with bipolar disorder showed a positive correlation among suicidality, depressive and manic symptoms, emotion dysregulation and insomnia (Table 3). In addition, it revealed a correlation with emotional impulsivity and difficulties in regulatory strategies. No correlations were found between suicidality and other variables considered (illness duration p = 0.77, positive family history for psychiatric illness p = 0.12, benzodiazepines: p = 0.55, antidepressants p = 0.32, neuroleptics: p = 0.42, mood stabilizers: p = 0.32, anxiety comorbidity p = 0.75).

The multiple-regression model including suicidality as the dependent variable, insomnia symptoms, manic /depressive, emotion dysregulation as independent variables, was significant (F = 6.2 p ≤ 0.0001) emotional impulsivity and manic symptoms remained significant.

3.2.3. Mediation analyses

We also postulated a mediation role for emotion dysregulation between insomnia symptoms and other factors considered, identifying the potential processes underneath. A mediation analysis was conducted with emotion dysregulation (DERS totals score) as the mediator between insomnia symptoms (ISI score) and depressive symptoms (BDI-II score). It revealed a mediation effect of emotion dysregulation

Table 3
Univariate and multivariate regression analyses on suicidality in subjects with bipolar disorder.

SSI	Univariate		Multivariate	
	B	p	B	p
ISI	0.29	0.008	0.17	0.098
DERS	0.07	0.023	0.09	0.132
DERS non acceptance	0.19	0.077	–	–
DERS goals-behaviors	0.27	0.072	–	–
DERS impulsivity	0.50	<0.001	0.38	0.032
DERS regulatory strategies	0.26	0.007	0.16	0.383
BDI-II	0.17	0.003	0.12	0.052
YMRS	0.36	0.001	0.31	0.003

Legend. Results of the univariate and multivariate regression analyses between the SSI: Scale for Suicide Ideation and the other variables considered. ISI: Insomnia Severity Index, DERS: Difficulties in Emotion Regulation Scale, DERS subscales: DERS Non Acceptance of emotion, DERS Difficulties in goals-behaviors, DERS impulsivity, DERS Difficulties regulatory strategies and other variables. BDI-II: Beck Depression Inventory, YMRS: Young Mania Rating Scale, B = unstandardized regression coefficient. Significance in bold.

(Z = 2.98, p = 0.004). Emotional impulsivity mediated the association between insomnia symptoms and suicidality (SSI score) (Fig. 1 Z = 2.07, p = 0.037). Non other mediation analyses were proved to be significant.

4. Discussion

We observed a sample of subjects diagnosed with bipolar disorder II during a depressive episode with mixed features and evaluated any insomnia symptoms, emotion dysregulation and suicidality, while considering their manic/depressive symptoms, current pharmacological therapy and other clinical/demographic factors that may contribute to mood disorders.

Our results confirm the view that insomnia symptoms may be important features in bipolar disorder. Patients with insomnia symptoms experienced a greater severity of depressive symptoms, greater difficulties in emotion regulation, notably impulsivity, and higher risk of suicidality compared to subjects without insomnia. Insomnia symptoms resulted significantly correlated with emotion dysregulation, emotional impulsivity and suicidality in subjects with bipolar disorder.

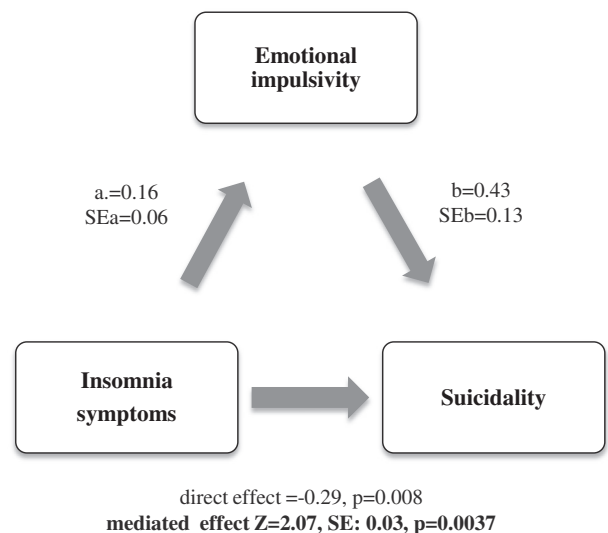


Fig. 1. Mediation analyses Emotional impulsivity mediated the association between insomnia symptoms and suicidality. a: unstandardized regression coefficient for the association between the independent variable and mediator, SEa = standard error of a. b: coefficient for the association between the mediator (in presence of independent variable) and the dependent variable, SEb = standard error of b. Z = Sobel test value. Significance in bold.

Of our sample, subjects with insomnia experienced depressive symptoms at a higher extent as previously observed [9] and higher difficulties with emotion regulation. In particular they showed difficulties in acceptance of emotion, in engaging in goal-directed behaviors, in impulse control and in limited access to effective regulatory strategies. These data may support previous evidence about the association between sleep disturbances and emotion dysregulation in bipolar patients during remitted phases [11,12]. Patients with insomnia also showed higher suicidality than patients without insomnia supporting data about the association of insomnia with suicidality [20,32].

In subjects with bipolar disorder emotion dysregulation was correlated not only with depressive symptoms, but also with insomnia symptoms. Interestingly, insomnia symptoms were correlated with difficulties in acceptance of emotion, in engaging in goal-directed behaviors, in impulse control and limited access to effective regulatory strategies. These data are consistent with previous evidence about the role of poor sleep quality and emotion dysregulation in bipolar patients [11,12].

In the same line, suicidality was related to manic, depressive symptoms and emotion dysregulation, especially to emotional impulsivity and to difficulties in regulatory strategies, as previously observed [47], but also to insomnia symptoms. Indeed, emotional impulsivity and manic symptoms were the factors more strongly related to suicidality.

Results of the mediation analyses confirmed the hypothesis of this study: emotion dysregulation may mediate the relationship between insomnia symptoms and bipolar symptoms, notably depressive symptoms and suicidality. In particular, emotional impulsivity might have a role in the relationship between insomnia and suicidality in subjects with bipolar disorder.

The present study may support evidence coming from experimental studies showing that sleep has important functions for the regulation of mood and emotion [48–51] while disturbed sleep, in particular insomnia, might lead to maladaptive emotional regulation, and consequently to exaggerated neural and behavioral reactivity to experiences [11,24,25,27]. Disturbed sleep has been linked to impulsive and aggressive behaviors [19,44] and consequently, to the increased risk of suicidality (for an overview see [20]).

Evidence proved an impairment in the top-down modulation of emotional processing when sleep is disturbed [27,28]: a dysfunction in the neural circuitry underlying emotion regulation was reported in individuals suffering from insomnia (for an overview see Riemann et al., [29]). Changes observed in brain structures in individuals with insomnia, such as a reduction in the volume of the prefrontal cortex and an increase in the amygdala volume [29], are in fact involved in enhanced emotional reactivity [21–23]. In addition, there is considerable evidence to suggest that sleep disruption impairs cognitive functioning involved in the decision making process including simple tasks. It might also affect high order cognitive processes, which are largely controlled by the neural activity within the prefrontal cortex [29,30]. Furthermore, some data suggests a reduced functional connectivity in individuals suffering from insomnia between parietal and medial prefrontal cortices related with an impairment in executive function [52]. This finding is substantiated through studies of experimental sleep loss which show that sleep disruption significantly reduces the functional connectivity in frontal brain regions, including the ventromedial regions involved in making decisions [30]. Likely, the impact of disturbed sleep on prefrontal cortical functioning contributes to loss of control over emotions, namely over the regulation of aggressive impulses with context-appropriate behaviors [19]. Insomnia symptoms may therefore be associated with amplified reactivity across the full range of affective valence. Therefore, they may potentially contribute to reported deficits in judgment and decision making related to sleep disruption [30,53].

The evaluation of sleep disturbances and namely of insomnia in subjects with bipolar disorder should be included in the routine clinical evaluation of subjects with bipolar disorder for its potential therapeutic implications and preventive treatment strategies with

long-term outcome. As already postulated, the treatment of sleep disturbances in bipolar disorder may improve the trajectory of the disorder [10,17]. Further research is needed to study the effect of the insomnia treatment on emotion dysregulation, impulsivity and suicidality in subjects with bipolar disorder.

Our results should be interpreted in light of several limitations including the lack of physiological measures of insomnia symptoms. Secondly, despite the use of mediation analyses, the cross-sectional design of the study limits any causal interpretation. Consequently, longitudinal studies are needed to examine the direction of risk and generalizability of the current findings.

In conclusion, this study suggests that: i) patients with bipolar disorder experiencing insomnia may hold a greater severity of mood symptoms, difficulties in emotion regulation and higher suicide risk compared to patients without insomnia; ii) insomnia symptoms may predict emotion dysregulation, particularly emotional impulsivity, difficulties in regulatory strategies and suicidality; iii) emotional impulsivity might play a mediating role in the relationship between insomnia and suicidality in subjects with bipolar disorder.

These findings may have clinical and therapeutical implications. In particular the assessment of insomnia in bipolar subjects should be a priority in order to identify those who may benefit from early insomnia intervention strategies.

Acknowledgement

None.

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.

References

- [1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. . Fifth edition (DSM-5) Washington: American Psychiatric Pub; 2013.
- [2] Wittchen HU. The burden of mood disorders. *Science* 2012;338:15.
- [3] Schaffer A, Isometsä ET, Tondo L, Moreno H, Turecki G, Reis C, et al. 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* 2015;17:1–6.
- [4] Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: findings from the global burden of disease study 2010. *Lancet* 2013;382:1575–86.
- [5] Ferrari AJ, Norman RE, Freedman G, Baxter AJ, Pirkis JE, Harris MG, et al. 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* 2014;9:91936.
- [6] Isometsä E. Suicidal behaviour in mood disorders—who, when, and why? *Can J Psychiatry* 2014;59:120–30.
- [7] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. . Washington Third edition (DSM-III) American Psychiatric Pub; 1980.
- [8] Gruber J, Miklowitz DJ, Harvey AG, et al. Sleep matters: Sleep functioning and course of illness in bipolar disorder. *J Affect Disord* 2011;134:416–20.
- [9] Geoffroy PA, Scott J, Boudebessé C, et al. Sleep in patients with remitted bipolar disorders: a meta-analysis of actigraphy studies. *Acta Psychiatr Scand* 2015;131:89–99.
- [10] Geoffroy PA, Micoulaud Franchi JA, Lopez R, et al. How to characterize and treat sleep complaints in bipolar disorders? *Encéphale* 2017;43:363–73.
- [11] Kanady JC, Soehner AM, Harvey AG. Retrospective examination of sleep disturbance across the course of bipolar disorder. *J Sleep Disord Ther* 2015;30:4.
- [12] Boudebessé C, Henry C. Emotional hyper-reactivity and sleep disturbances in remitted patients with bipolar disorders. *Encéphale* 2012;38:173–8.
- [13] Etain B, Godin O, Boudebessé C, Aubin V, Azorin JM, Bellivier F, et al. Sleep quality and emotional reactivity cluster in bipolar disorders and impact on functioning. *Eur Psychiatry* 2017;45:190–7.
- [14] Ritter PS, Höfler M, Wittchen HU, et al. Disturbed sleep as risk factor for the subsequent onset of bipolar disorder—data from a 10-year prospective-longitudinal study among adolescents and young adults. *J Psychiatr Res* 2015;68:76–82.
- [15] Ritter PS, Marx C, Lewtschenko N, et al. The characteristics of sleep in patients with manifest bipolar disorder, subjects at high risk of developing the disease and healthy controls. *J Neural Transm* 2012;119:1173–84.
- [16] Ritter PS, Marx C, Bauer M, Leopold K, Pfennig A. The role of disturbed sleep in the early recognition of bipolar disorder: a systematic review. *Bipolar Disord* 2011;13:227–37.

- [17] Harvey AG, Kaplan KA, Soehner AM. Interventions for sleep disturbance in bipolar disorder. *Sleep Med Clin* 2015;10:101–5.
- [18] Pompili M, Innamorati M, Forte A, et al. Insomnia as a predictor of high-lethality suicide attempts. *Int J Clin Pract* 2013;67:1311–6.
- [19] Kamphuis J, Dijk DJ, Spreen M, Lancel M. The relation between poor sleep, impulsivity and aggression in forensic psychiatric patients. *Physiol Behav* 2014;123 (168–7).
- [20] Woznica AA, Carney CE, Kuo JR, Moss TG. The insomnia and suicide link: toward an enhanced understanding of this relationship. *Sleep Med Rev* 2015;22:37–46.
- [21] Gross JJ, Thompson RA. Emotion regulation: conceptual foundations. In: Gross JJ, editor. *Handbook of emotion regulation*. New York, NY, USA: Guilford Press; 2011.
- [22] Henry C, Phillips M, Leibenluft E, M'Bailara K, Houenou J, Leboyer M. Emotional dysfunction as a marker of bipolar disorders. *Front Biosci* 2012;4:2622–30.
- [23] Hofmann SG, Sawyer AT, Fang A, Asnaani A. Emotion dysregulation model of mood and anxiety disorders. *Depress Anxiety* 2012;29:409–16.
- [24] Baglioni C, Spiegelhalder K, Lombardo C, Riemann D. Sleep and emotions: a focus on insomnia. *Sleep Med Rev* 2010;14:227–38.
- [25] Altena E, Micoulaud-Franchi JA, Geoffroy PA, Sanz-Arigita E, Bioulac S, Philip P. The bidirectional relation between emotional reactivity and sleep: from disruption to recovery. *Behav Neurosci* 2016;130:336–50.
- [26] Riemann D, Nissen C, Palagini L, Otte A, Perlis ML, Spiegelhalder K. The neurobiology, investigation, and treatment of chronic insomnia. *Lancet Neurol* 2015;14:547–58.
- [27] Yoo SS, Gujar N, Hu P, Jolesz FA, Walker MP. The human emotional brain without sleep—a prefrontal amygdala disconnect. *Curr Biol* 2007;17:877–8.
- [28] Krause AJ, Simon EB, Mander BA, et al. The sleep-deprived human brain. *Nat Rev Neurosci* 2017;18:404–18.
- [29] Rossa KR, Smith SS, Allan AC, Sullivan KA. The effects of sleep restriction on executive inhibitory control and affect in young adults. *J Adolesc Health* 2014;55:287–92.
- [30] Van Someren EJ, Cirelli C, Dijk DJ, Van Cauter E, Schwartz S, Chee MW. Disrupted sleep: from molecules to cognition. *J Neurosci* 2015;35:13889–95.
- [31] Acheson A, Richards JB, de Wit H. Effects of sleep deprivation on impulsive behaviors in men and women. *Physiol Behav* 2007;91:579–87.
- [32] McCall WV, Black CG. The link between suicide and insomnia: theoretical mechanisms. *Curr Psychiatry Rep* 2013;15(9):389.
- [33] First MB, Williams JBW, Karg RS, Spitzer RL. In: Fossati Andrea, Borroni Serena, editors. *SCID-5-CV. Intervista Clinica Strutturata per i Disturbi del DSM-5. Versione per il Clinico*. Milano: Raffaello Cortina Editore; 2017 Italiana a cura di.
- [34] *Insomnia Morin CM. Psychological assessment and management*. New York: Guilford Press; 1993.
- [35] Gratz KL, Roemer L. Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation of the difficulties in emotion regulation scale. *J Psychopathol Behav Assess* 2004;30:315.
- [36] Sighinolfi C, Norcini Pala A, Rocco Chiri L, Marchetti I, Sica C. Difficulties in emotion regulation scale (DERS): Traduzione e adattamento italiano. *Psicoterapia Cognitiva e Comportamentale* 2010;1:1–44.
- [37] Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the scale for suicide ideation. *J Consult Clin Psychol* 1979;47:343.
- [38] Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck depression inventories -IA and -II in psychiatric outpatients. *J Pers Assess* 1996;67:588–97.
- [39] Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* 1978;133:429.
- [40] Spormaker VI, Verbeek I, van den Bout J, Klip EC. Initial validation of the SLEEP-50 questionnaire. *Behav Sleep Med* 2005;3:227.
- [41] Measso G, Cavarzeran F, Zappalà G. *Dev Neuropsychol* 1993;9:77–85.
- [42] Castronovo V, Galbiati A, Marelli S, Brombin C, Cugnata F, Giarolli L, et al. Validation study of the Italian version of the insomnia severity index (ISI). *Neurol Sci* 2016;37:1517–24.
- [43] Ghisi M, Flebus GB, Montano A, Sanavio E, Sica C. *Beck Depression Inventory-II. Manuale Italiano*. Firenze: Giunti Editore; 2006.
- [44] Palma A, Pancheri P. Scale di valutazione e di misura dei sintomi psichiatrici. In: Cassano GB, Pancheri P, et al, editors. *Trattato Italiano di Psichiatria*. Seconda edizione. Milano: Masson Italia; 1999.
- [45] Conti L. *Repertorio delle scale di valutazione in psichiatria (SEE Firenze)*; 1999.
- [46] Sobel ME. Asymptotic confidence intervals for indirect effects in structural equation models. *Sociol Methodol* 1982;13:290–312.
- [47] Johnson SL, Carver CS, Tharp JA. Suicidality in bipolar disorder: the role of emotion-triggered impulsivity. *Suicide Life Threat Behav* 2017;47:177–92.
- [48] Walker MP, van der Helm E. Overnight therapy? The role of sleep in emotional brain processing. *Psychol Bull* 2009;135:731–4.
- [49] Walker MP. The role of sleep in cognition and emotion. *Ann N Y Acad Sci* 2009;1156:168–97.
- [50] Goldstein AN, Walker MP. The role of sleep in emotional brain function. *Annu Rev Clin Psychol* 2014;10:679–708.
- [51] Fairholme CP, Mamber R. Sleep, emotions, and emotion regulation: an overview. *Sleep and affect*. Amsterdam: Elsevier; 2015.
- [52] Li Y, Wang E, Zhang, et al. Functional connectivity changes between parietal and prefrontal cortices in primary insomnia patients: evidence from resting-state fMRI. *Eur J Med Res* 2014;19:32.
- [53] Perogamvros L, Schwartz S. Sleep and emotional functions. *Curr Top Behav Neurosci* 2015;25:411–31.