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Relationship between anhedonia, biological rhythms, functioning and depression severity in patients with bipolar disorder

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Summary

Aim. The purpose of this study was to examine relationship between anhedonia, disruption of biological rhythms, functioning and depression severity in patients with bipolar disorder (BD).

Material and methods. The sample included 58 patients with bipolar depression aged 18–65 years. The participants were assessed using the following scales: Dimensional Anhedonia Rating Scale (DARS), Snaith-Hamilton Pleasure Scale (SHAPS), Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR), Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN), Functioning Assessment Short Test (FAST). Correlations between the variables were calculated. We built linear regression models with FAST or QIDS-SR as a dependent variable. Mediation analysis was performed.

Results. Statistically significant correlations were observed between the included variables. Biological rhythms dysregulation and anhedonia were independent predictors of the level of functioning or depression severity. Mediation analysis demonstrated statistically significant mediation of the relationship between anhedonia and depression severity/functioning by the BRIAN score.

Conclusions. We demonstrated for the first time the interactions between anhedonia, dysregulation of biological rhythms and functioning/depression severity in patients with BD. Reward deficits by causing disruption of rhythm of daily activities and social contacts may result in more difficulties in functioning and higher intensity of depressive symptoms.

Key words: bipolar disorder, anhedonia, biological rhythm

Introduction

Disruptions of biological rhythms are considered to play an etiological role in bipolar disorder (BD) [1]. Dysregulations in various circadian rhythms have been described not only in manic or depressive states, but also in euthymia [2–7] and have been linked with poorer functioning and lower quality of life in bipolar patients [2, 8, 9]. Genes involved in the regulation of circadian rhythms (the so called clock genes) have been associated with the pathophysiology of BD [10]. Medications can potentially influence biological rhythms, with lithium having the largest amount of data – evidence from animal and human studies demonstrate that lithium may improve circadian dysfunctions and stabilize daily rhythms, which can contribute to its therapeutic actions [11–13].

The suprachiasmatic nucleus (SCN) located in the anterior hypothalamus is the brain's principal "pacemaker" which generates circadian rhythms distributed to other systems in the body [13, 14]. The activity of SCN is synchronized and modulated by the so called *zeitgebers* – external, environmental stimuli like light, temperature, timing of meals, work, social interactions, exercise [2, 14–16]. According to the "social zeitgeber theory", factors which disrupt schedules of social activities or contacts can trigger abnormalities in the circadian rhythms and thus lead to the occurrence of symptoms of mood disorders in vulnerable individuals [17, 18].

Another hypothesis links biological rhythms to reward system – stressors can deactivate the reward system, cause neglect of social activities and eventually lead to depressive episodes. The opposite can happen in manic episodes when overactivation of the reward system induce disruption of social and circadian rhythms [17]. This relationship may be bidirectional – dysregulations in circadian rhythms potentially affect the reward system [19]. Moreover, SCN sends projections to the mesolimbic dopaminergic pathways and clock genes are expressed in areas of the reward system (e.g., ventral tegmental area, ventral striatum, prefrontal cortex) [20–23].

Thus, the associations between the reward system, biological rhythms and functioning in mood disorders are complex and neurobiologically interconnected. Anhedonia is one of the core symptoms of depression, defined as diminished interest or pleasure in activities [24], and reflects dysfunctions in the reward system of the brain [25]. To the best of our knowledge, no previous study has evaluated the relationship between anhedonia, disruptions of the biological rhythms and functioning in BD. Therefore, the aim of our project was to perform a complex analysis of those clinical features in patients with bipolar depression, including mediation analysis to examine potential effect of anhedonia on functioning or symptom severity by biological rhythms dysregulation.

We hypothesized that: (1) both anhedonia and rhythm disruptions are independent predictors of worse functioning and higher depression severity in BD depressed patients; (2) biological rhythm dysregulations mediate the effect of reward deficiencies on functioning and severity of depressive symptoms.

1. Material and methods

1.1. Participants

Patients from the Department of Adult, Child and Adolescent Psychiatry, University Hospital in Krakow (in – and outpatients) were enrolled in the study if they met the inclusion criteria: age 18–65 years; DSM-5 diagnosis of BD in depressive episode; no unstable or severe medical illness; no substance use disorder (apart from nicotine or caffeine) in the last 12 months. As psychiatric comorbidities are common in patients with BD [26], we decided not to exclude patients with additional diagnoses (anxiety disorders, personality disorders, eating disorders, attention deficit hyperactivity disorder [ADHD]) provided their intensity was not severe (i.e., not impairing functioning markedly and not being the current main reason for seeking medical assistance).

Minimal sample size was established as 47 and was calculated using the following assumptions: $\alpha = 0.05$; $\beta = 0.20$ (power = 80%); $r = 0.4$. We assumed the minimal clinically important correlation coefficient as 0.4 in order to detect at least moderate correlations between variables [27].

The study was approved by the Bioethics Committee of the Jagiellonian University in Krakow, Poland. The recruitment lasted from January 2020 until August 2022. All participants provided informed, written consent to take part in the study.

1.2. Measures

The DARS (*Dimensional Anhedonia Rating Scale*) is a self-administered 17-item scale with four categories – hobbies, foods/drinks, social activities, and sensory experiences. For each category the respondents give a few examples of their favourite activities/experiences and evaluate their interest, motivation, desire and pleasure "right now" with a 5-point Likert scale ("Not at all" = 0; "Slightly" = 1; "Moderately" = 2; "Mostly" = 3; "Very much" = 4). The final score is a sum of all items (score range: 0–68) and lower scores indicate higher severity of anhedonia [28]. The DARS assesses deficits in various components of the reward processing – consummatory and motivational anhedonia [29]. The Polish adaptation of the scale was recently validated by our team in a population of patients with mood disorders and healthy controls – it demonstrated very good psychometric properties: strong internal consistency for the DARS total score (Cronbach's $\alpha = 0.95$) and all subscales (0.86–0.93), good convergent and divergent validity [30].

The SHAPS (*Snaith-Hamilton Pleasure Scale*) is a self-administered scale with 14 items assessing pleasure from different experiences. Each question contains four responses: "strongly agree", "agree" (both rated 0 points), "disagree", and "strongly disagree" (both rated 1 point). Total score ranges between 0 and 14 points – higher scores indicate more severe anhedonia [31]. The Polish translation of the scale has demonstrated excellent reliability (0.913) [32].

We decided to include two instruments measuring anhedonia as they measure different aspects of the reward processing deficits – the SHAPS evaluates only con-

summatory anhedonia whereas the DARS assesses also desire, motivation and effort [28]. The strategy to use more than one tool for the assessment is supported by studies which indicate low overlap between scales measuring affective symptoms [33, 34].

The QIDS-SR (*Quick Inventory of Depressive Symptomatology –Self Report*) is a 16-item tool based on the DSM criteria for MDD and measures severity of depressive symptoms. The total score ranges between 0 and 27 points with higher scores indicating more severe depression [35].

The BRIAN (*Biological Rhythms Interview of Assessment in Neuropsychiatry*) is a self-report questionnaire measuring rhythm disruptions during "the last 15 days" in four areas (overall 18 items): sleep, activity, social rhythm, eating patterns [36]. All items are rated on a 4-point scale. The total score ranges between 18 and 72 points, where higher scores indicate more severe disturbance of biological rhythms. Both the original BRIAN and its Polish adaptation have been validated in clinical samples of BD patients [36, 37].

The FAST (*Functioning Assessment Short Test*) is a brief instrument administered by a trained clinician and designed to measure functioning difficulties in psychiatric patients, originally validated in bipolar patients. The scale contains 24 items which rate impairment in six domains of functioning (in the last 15 days before assessment): autonomy, occupational functioning, cognitive functions, financial issues, interpersonal relationships, and leisure time. All items are rated on a 4-point scale, where higher total scores indicate more serious functional impairment [38].

1.3. Procedures

Patients included in the study were evaluated during a single visit to the Department of Psychiatry. A trained clinician performed the medical interview to verify the diagnosis of bipolar depression and psychiatric comorbidities (according to the DSM-5 criteria). In order to verify the inclusion criteria, the patients were assessed with a structured psychiatric interview (*Mini International Neuropsychiatric Interview* – MINI [39]). Sociodemographic and medical data were collected. Participants were asked to fill in the following questionnaires: DARS, SHAPS, QIDS-SR, BRIAN. The FAST was filled by a clinician.

1.4. Statistical analysis

Basic clinical and socio-demographic data for the studied group were presented as percentages (for nominal data), mean and standard deviation (*SD*) (for quantitative data with normal distribution) or median with interquartile range (IQR) (for non-normally distributed quantitative data). Assessment of normality was conducted by the analysis of histograms and *z*-scores for skewness and kurtosis – with values <1.96 indicating approximation of the normal distribution.

We conducted reliability analysis for the items in the FAST scale (as the Polish translation of this tool has not been validated in patients with mood disorders before). Internal consistency (reliability measure) was performed using Cronbach's α (with values above 0.7 considered acceptable).

Correlations between anhedonia measures (DARS [total score and subscales] or SHAPS), BRIAN (total and subscales), FAST, and QIDS-SR were calculated. Pearson's or Spearman's rank correlation coefficient was selected depending on the normality of distribution of the variables.

Linear regression models were built with functioning (measured by the FAST) or depression severity (measured by the QIDS-SR) as dependent variables. For the models with the QIDS-SR, rhythms disruptions (BRIAN), anhedonia (assessed by the DARS or SHAPS) and lithium treatment were chosen as predictors (lithium treatment was added due to its potential impact on biological rhythms, as already mentioned in the introduction part). As bipolar disorder is progressive and patients in later stages of the disease experience deterioration of functioning, we examined the correlations between the FAST and: age, duration of illness, number of previous episodes. No statistically significant correlations were observed for age or duration of illness ($rs = 0.157$; $p = 0.315$ and $rs = 0.234$; $p = 0.130$, respectively). Therefore these variables were not included in the regression models. Significant correlations between the FAST and the number of previous affective episodes was observed ($rs = 0.325$; $p = 0.049$). Models with the FAST as a dependent variable, anhedonia (DARS or SHAPS), biological rhythms disruptions and the QIDS-SR, lithium treatment or number of affective episodes as independent variables were built.

Forced entry was selected as a method of entering predictors into the model. The following basic assumptions of the linear model were checked: (1) linearity (assessed by scatterplots of the dependent variable and each predictor); (2) homoscedasticity, normality and linearity of residuals (evaluated by analysis of histograms for the residuals and plots of standardized predicted values vs. standardized residuals). Data were inspected for outliers and influential cases (assessed by analysis of Cook's distance, Mahalanobis distance and average leverage) [40]. Potential collinearity was checked by computation of the variance inflation factor (VIF) – values >10 indicate collinearity.

Mediation analysis was performed in order to estimate the indirect effect of anhedonia on the level of functioning or depression severity through biological rhythms dysregulation as a mediator (measured by the BRIAN scale).

Statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) version 28.0. The PROCESS tool (extension to SPSS) was used to perform the mediation analysis. The level of significance was set at $p < 0.05$.

2. Results

2.1. Sample characteristics

58 BD patients in a current depressive episode were included in the study. Basic socio-demographic and clinical data are presented in Table 1. Patients were on different pharmacotherapy regimens but only treatment with lithium was included as a variable in the analysed models due to the evidence that it can impact daily rhythms.

Table 1. **The basic socio-demographic and clinical characteristics of the studied population; distributions of the scores of anhedonia (DARS and SHAPS), depression (QIDS-SR), rhythms disruptions (BRIAN), and functioning (FAST) in the studied group**

Age (years: median; IQR)	35 (20)
Gender (% of females)	62.1 %
Education level (% of higher degree completed)	62.1 %
Duration of illness; (years: median; IQR)	7 (12)
Number of previous affective episodes (median; IQR)	7 (4.8)
Past depressive episodes	4 (3)
Past maniac/hypomanic episodes	3 (2)
Duration of the current depressive episode (months; median; IQR)	4 (4)
Smoking (% yes)	36.2 %
BMI (kg/m^2; median; IQR)	25 (6.7)
Bipolar type	
Type I	19.0 %
Type II	74.1 %
Bipolar spectrum	6.9 %
Lithium therapy (% yes)	24.1 %
DARS (mean; SD)	39.6 (15)
SHAPS (median; IQR)	4.5 (7)
QIDS-SR (mean; SD)	13.8 (5.7)
BRIAN (n = 54)	
Total (mean; SD)	51.9 (8.5)
Sleep (mean; SD)	14.4 (2.8)
Activity (mean; SD)	15.6 (3.4)
Social (mean; SD)	10.2 (3.2)
Eating (median; IQR)	12 (5.8)
FAST (mean; SD) (n = 47)	35.7 (15.7)

IQR – interquartile range, SD – standard deviation

Table 1 also shows the results of psychometric evaluation in the studied bipolar population. The mean QIDS-SR score in our sample was 13.8 which indicates moderate depression [41]. Median SHAPS of 4.5 is above the cut-off point of 2 points (which provided the best discrimination between normal state and anhedonia in the paper publishing this scale) [31]. Also the mean FAST score was above the cut-off point of 11 points, indicating functional impairment [38]. The reliability of Polish FAST was excellent, with the Cronbach's α value of 0.927.

Correlations between the variables were calculated and the results are presented in Table 2. Statistically significant correlations were observed between the BRIAN

(total score), two of its subscales ("Activity" and "Social"), FAST, QIDS-SR and the anhedonia measures (SHAPS, DARS – total score and most of subscales).

Table 2. **Correlation coefficients between anhedonia measures (DARS, SHAPS) and biological rhythms disruptions (BRIAN), difficulties in functioning (FAST), depression severity (QIDS-SR)**

	DARS-total	DARS-hobbies	DARS-Food/ drink	DARS-social	DARS-sensory	SHAPS
BRIAN-total	-0.392**,p	-0.176	-0.428**	-0.462**,p	-0.335*	0.481**
BRIAN-Sleep	-0.075p	0.053	-0.176	-0.130p	0.049	0.107
BRIAN-Activity	-0.543**,p	-0.336*	-0.456**	-0.579**,p	-0.439**	0.576**
BRIAN-Social	-0.453**,p	-0.260	-0.452**	-0.481**,p	-0.470**	0.423**
BRIAN-Eating	-0.153	0.005	-0.124	-0.105p	-0.090	0.270
FAST	-0.406**,p	-0.202	-0.316*	-0.483**,p	-0.421**	0.511**
QIDS-SR	-0.482**,p	-0.305*	-0.310*	-0.503**,p	-0.397**	0.703**

* <0.05; ** <0.01; p – Pearson's correlation coefficient (the remaining coefficients were calculated as Spearman's correlation coefficient due to lack of normal distribution of at least one variable)

2.2. Regression models

Linear regression models were built with difficulties in functioning (FAST) as a dependent variable with anhedonia (measured by the DARS or SHAPS), biological rhythms disruptions (BRIAN) and depression severity (QIDS-SR) as predictors. Additional models with lithium therapy or the number of previous affective episodes as predictors were also built (Table 3).

Table 3. **Linear regression models with functioning as a dependent variable (FAST) and anhedonia (DARS or SHAPS), biological rhythm dysregulation (BRIAN) and depression severity (QIDS-SR) or lithium therapy or number of previous affective episodes as predictors**

	b	SE	β	p
DARS	-0.231	0.153	-0.226	0.139
BRIAN	0.757	0.298	0.401	0.015
QIDS-SR	0.169	0.474	0.060	0.724
$R^2 = 0.32$, $p_{model} < 0.001$				
SHAPS	1.897	0.744	0.473	0.015
BRIAN	0.744	0.284	0.394	0.012
QIDS-SR	-0.496	0.557	-0.177	0.378
$R^2 = 0.38$, $p_{model} < 0.001$				
DARS	-0.095	0.160	-0.093	0.557

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BRIAN	1.065	0.305	0.535	0.001
Lithium (1 – yes; 2 – no)	-9.959	5.169	-0.285	0.061
$R^2 = 0.37$, $p_{model} < 0.001$				
SHAPS	0.967	0.650	0.240	0.144
BRIAN	0.870	0.321	0.437	0.010
Lithium (1 – yes; 2 – no)	-8.272	4.938	-0.237	0.102
$R^2 = 0.39$, $p_{model} = 0.003$				
DARS	-0.196	0.173	-0.186	0.265
BRIAN	0.784	0.288	0.420	0.010
Number of previous episodes	0.375	0.401	0.144	0.356
$R^2 = 0.34$, $p_{model} < 0.001$				
SHAPS	1.347	0.636	0.335	0.042
BRIAN	0.648	0.284	0.347	0.029
Number of previous episodes	0.310	0.375	0.119	0.413
$R^2 = 0.39$, $p_{model} < 0.001$				

b – unstandardized coefficient; SE – standard error; β – standardized coefficient; R^2 – coefficient of determination

All models were statistically significant. When depression severity was included in the model, biological rhythms dysregulation and anhedonia measured by the SHAPS were significant predictors of the level of functioning (with higher rhythm disruption and higher anhedonia predicting more difficulties in functioning). When the DARS was included as the measure of anhedonia, only the BRIAN was a significant independent variable.

When lithium treatment was one of the variables (instead of depression severity) only the biological rhythms dysregulation significantly predicted the level of functioning (anhedonia lost significance). If the number of previous affective episodes was included in the models, disruption of biological rhythms and anhedonia (measured by the SHAPS) were statistically significant predictor of the FAST total score.

Another linear regression models were built with depression severity (QIDS-SR) as a dependent variable, anhedonia (DARS or SHAPS), biological rhythms disruptions and lithium treatment as predictors (Table 4).

Table 4. **Linear regression model with depression severity as a dependent variable (QIDS-SR) and anhedonia (DARS or SHAPS), biological rhythm dysregulation (BRIAN) and lithium therapy as predictors**

	b	SE	β	p
DARS	-0.118	0.048	-0.331	0.017
BRIAN	0.281	0.085	0.428	0.002

table continued on the next page

Lithium (1 – yes; 2 – no)	0.237	1.484	0.020	0.874
$R^2 = 0.41$, $p_{model} < 0.001$				
SHAPS	0.953	0.159	0.637	<0.001
BRIAN	0.171	0.074	0.243	0.026
Lithium (1 – yes; 2 – no)	0.834	1.205	0.065	0.493
$R^2 = 0.61$, $p_{model} < 0.001$				

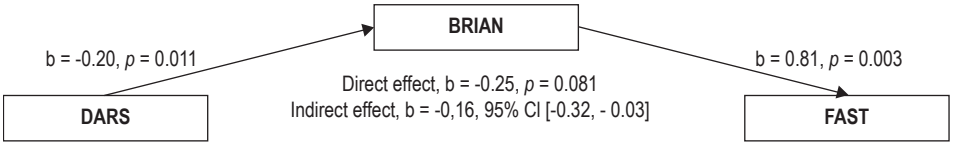
b – unstandardized coefficient; SE – standard error; β – standardized coefficient; R^2 – coefficient of determination

Anhedonia (regardless of the psychometric tool used for assessment) and dysregulation of biological rhythms were independent significant predictors of the severity of depression, with models explaining up to 61% of variance of the dependent variable. Higher anhedonia (indicated by lower DARS and higher SHAPS scores) and greater disruption of biological rhythms were predictors of higher depression severity.

2.3. Mediation analysis

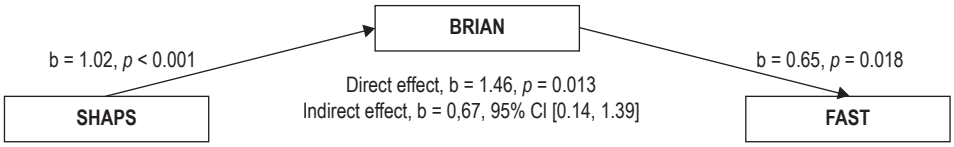
Mediation analysis was used to estimate indirect effects of anhedonia (measured by the DARS or SHAPS) on functioning (FAST) through dysregulation of biological rhythms (BRIAN). The diagrams of mediation are presented below (Figure 1 and Figure 2). Significant mediation was observed for both models – after including dysregulation of biological rhythms, the direct effect of anhedonia on functioning was: (1) no longer significant when the DARS was used as a measurement tool; (2) weaker vs. no mediator included in the model (when the SHAPS was used as a predictor).

Mediation analysis was also used to estimate indirect effects of anhedonia (measured by the DARS or SHAPS) on depression severity (QIDS-SR) through dysregulation of biological rhythms (BRIAN). The diagrams of mediation are presented below (Figure 3 and Figure 4). Significant mediation was observed for both models – after including dysregulation of biological rhythms, the effect of anhedonia on depression severity was weaker compared to the total effect (without the mediator).



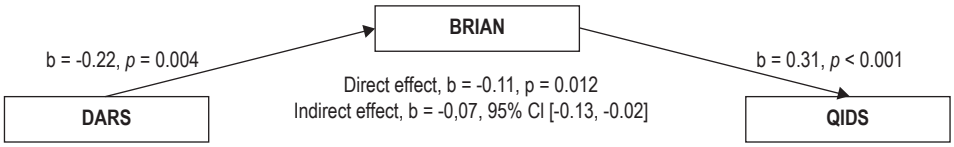
b – regression coefficients; 95% CI – 95% confidence interval calculated using bootstrapping on 5,000 samples

Figure 1. **Model of anhedonia (DARS) as a predictor of the level of functioning (FAST), mediated by biological rhythm dysregulation (BRIAN)**



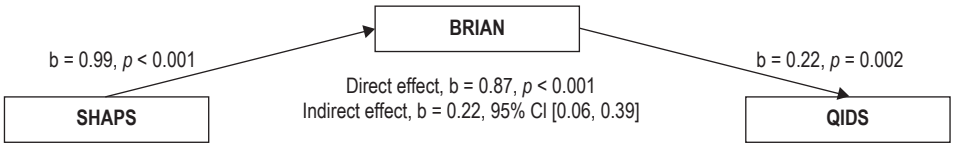
b – regression coefficients; 95% CI – 95% confidence interval calculated using bootstrapping on 5,000 samples

Figure 2. **Model of anhedonia (SHAPS) as a predictor of the level of functioning (FAST), mediated by biological rhythm dysregulation (BRIAN)**



b – regression coefficients; 95% CI – 95% confidence interval calculated using bootstrapping on 5,000 samples

Figure 3. **Model of anhedonia (DARS) as a predictor of depression severity (QIDS-SR) mediated by biological rhythm dysregulation (BRIAN)**



b – regression coefficients; 95% CI – 95% confidence interval calculated using bootstrapping on 5,000 samples

Figure 4. **Model of anhedonia (SHAPS) as a predictor of depression severity (QIDS-SR) mediated by biological rhythm dysregulation (BRIAN)**

3. Discussion of results

In this paper we demonstrated for the first time the tripartite interactions between anhedonia, dysregulation of biological rhythms and functioning/depression severity in patients with bipolar disorder. Our results indicate an important role of biological rhythms in the described phenomena.

We observed significant moderate correlations between the disruption of biological rhythms and anhedonia (correlation coefficients – 0.392 and 0.481 for the DARS and the SHAPS respectively). However, not all of the BRIAN subscales were significantly correlated with anhedonia measures – only coefficients for the "Activity" and "Social" subscales reached statistical significance. The highest, strong correlations were observed between the BRIAN-activity subscale and the DARS or SHAPS (-0.543 and 0.576

respectively). The analysis of specific DARS subscales indicated that anhedonia in the areas of "eating/drinking", "social activities" and "sensory experiences" had the strongest correlation with biological rhythms dysregulation. The "Activity" subscale of the BRIAN asks responders about difficulties in maintaining rhythm of home activities, work duties, physical and sexual activity whereas the "Social" subscale contains questions about contacts and communication with other people. It can be hypothesized that deficits in consumption or motivation may lead to neglect of different activities and disturb regularity of, i.a., work activities, entertainment, social contacts, sports.

Interestingly, anhedonia (measured by the SHAPS) and biological rhythm dysregulation were independent predictors of the level of functioning, even adjusted for the severity of depressive symptoms (assessed by the QIDS-SR) or the number of previous affective episodes. It has been observed by other authors that biological rhythms disturbance can be an independent predictor of functional impairment [2, 8, 9] but to the best of our knowledge, so far nothing has been published on the additional relationship of these features with anhedonia. Mediation analysis demonstrated complete mediation for the relationship between the BRIAN, DARS and FAST – the effect of anhedonia (measured by the DARS) on the level of functioning was no longer statistically significant when dysregulation of biological rhythms was included as a mediator. When lithium treatment was included as one of the predictors of functioning, rhythms dysregulation remained significant, but anhedonia lost significance.

Both anhedonia (regardless of the measurement tool) and biological rhythms disruptions were independent predictors of depression severity (adjusted for lithium treatment), with models explaining relatively high percent of variance in the dependent variable (41% when the DARS was included in the model and 61% for the SHAPS). Mediation analysis demonstrated statistically significant mediation of the relationship between anhedonia and depression severity by the BRIAN total score. The association between disturbances in biological rhythms and the severity of depression in patients with BD has been observed [2, 42, 43], but it has not been examined in the context of anhedonia.

Amongst all the DARS subscales, the "Social" subscale had the highest correlation with dysregulation of biological rhythms, the FAST and QIDS-SR scorers in our study. This observation is in line with the already mentioned in the introduction theory of "social zeitgebers", according to which neglect of social activities can lead to insufficient external zeitgebers, disrupted circadian rhythms and eventually occurrence of depression or functional impairment [4, 17, 18]. Based on the results of our study, it can be speculated that disturbances in social rhythms are a mediator between anhedonia and depression severity/functioning. Our research adds to the theory of the "integrated reward/circadian rhythm model" which postulates, i.a., that deactivation/activation of the behavioural approach system leads to desensitisation/sensitisation of the reward system, disruption of social routines and circadian rhythms, and consequently to depressive/hypomanic symptoms [4, 17, 22, 44]. One of the chronotherapeutic interventions related to the above mentioned theories is the interpersonal and social rhythm therapy (IPSRT) [45]. The goal of this therapy is to monitor and stabilise regularity of daily activities and social contacts. Studies (including randomised controlled

trials) have demonstrated utility of IPSRT in the acute and maintenance treatment of bipolar depression and improvement in psychosocial and occupational functioning of bipolar patients [15, 46].

Our study has a few limitations: (1) cross-sectional design of the study – causality and the direction of the studied interactions cannot be proven by our research; (2) patients with other psychiatric conditions were included (however, comorbidity is frequent in the population of patients with BD and not limiting our sample to only one diagnosis makes it more naturalistic) [26]; (3) patients were on different pharmacotherapy regimens which potentially could have influenced their scores (we included lithium treatment in our regression models due to the evidence of its potential role in circadian rhythms regulation); (4) no definite conclusion about circadian dysregulation can be made as we did not study objective markers of circadian rhythm (like melatonin levels).

4. Conclusions

In conclusion, we observed significant interactions between anhedonia, dysregulation of biological rhythms and the level of functioning or depression severity. Our study can lead to a hypothesis that reward deficits by causing disruption of daily activities and social contacts result in worse functioning and more severe depression. Further studies with longitudinal design and including circadian rhythm biomarkers are needed to better understand these complex interactions.

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