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## RESEARCH ARTICLE

### Biological Rhythms in People from North Macedonia with Bipolar Disorder: Application of the Macedonian Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN)

Goce Kalcev<sup>1\*</sup>, Ivan Barbov<sup>2</sup>, Pavlina Ilieska Kotevska<sup>3</sup>, Antonio Preti<sup>4</sup> and Mauro G. Carta<sup>5</sup>

<sup>1</sup>International Ph.D. in Innovation Sciences and Technologies, University of Cagliari, Cagliari, Italy

<sup>2</sup>University Clinic of Neurology, Skopje, North Macedonia

<sup>3</sup>Public Health Institution, Psychiatric Hospital Demir Hisar, North Macedonia

<sup>4</sup>Department of Neuroscience, University of Turin, Italy<sup>5</sup>Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy

#### Abstract:

##### Objective:

The Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) is a tool aimed at clinically evaluating disturbances in biological rhythm. In this study, we examined the reliability and validity of the Macedonian version of the BRIAN.

##### Methods:

A total of 100 participants, including 50 subjects with bipolar disorder (BD) and 50 control healthy subjects, were recruited. Construct validity was tested by comparing the mean BRIAN scores of the BD patients and control subjects.

##### Results:

No difference by gender or age was noticed, but patients differed from controls in education and occupation. Reliability, as measured with Cronbach's alpha, was good in BD individuals, except for the Rhythms subscale. Reliability in controls was less good, especially for the Sleep and Rhythms subscales. The tool was able to discriminate patients with controls, with large differences on all subscales. However, since the reliability was suboptimal for some of these subscales, these differences cannot be entirely trusted.

##### Conclusion:

The study suggests that the Macedonian version of this instrument has good psychometric characteristics and also encourages the chance of developing mixed screening tools by incorporating elements of biological rhythm dysregulation into the routine evaluation of mood.

**Keywords:** Bipolar disorder, BRIAN, Macedonian BRIAN, Disturbances, Biological rhythms, Mood.

#### Article History

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## 1. INTRODUCTION

Bipolar disorder (BD) affects 2-4% of the population and is one of the major causes of disability. The course of bipolar disorder is cyclical and identified by episodes of depression and (hypo)mania with or without mixed features, accompanied by or in the absence of interepisodic euthymia [1]. Alterations in biological rhythms (BR) may have a role in the pathophysiology of BD and may serve as a possible marker in the identification of early stages and relapses of this disturbance as well [2]. Many studies have assumed that

identifying the link between biological rhythm disturbances and BD might help better clarify its etiology [3]. Indeed, a vast amount of literature explains the relationship between disruptions of biological rhythms and the maintenance, remission and treatment of bipolar episodes [4 - 8].

The Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) was developed to clinically approach disturbances in biological rhythm, especially in patients with mental disorders [9, 10]. Hence, a biological rhythm assessment is not only cardinal for identifying the cause of clinical symptoms but as well for the psychiatric treatment and clinical research of mood disorders. The Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) is an 18-item interviewer

\* Address correspondence to this author at the International Ph.D. in Innovation Sciences and Technologies, University of Cagliari, Cagliari, Italy;  
E-mail: gocekcalcev@yahoo.com

administered instrument that focuses on appraising four main areas related to circadian rhythm disturbance, concretely: sleep, activities, social rhythms and eating patterns. Items are estimated using a 4-point scale, (1)=no difficulty, (2)=mild difficulty, (3)=moderate difficulty, and (4)=severe difficulty. The BRIAN scores, therefore, range from 1 to 72, where the higher scores indicate serious circadian rhythm disturbance [11].

The objective of this study was to examine the reliability and validity of the Macedonian version of the BRIAN by investigating the relevance of the scale for identifying circadian rhythm abnormalities in subjects with BD compared with the healthy subjects in a Macedonian population.

## 2. MATERIALS AND METHODS

The 1995 Declaration of Helsinki and its revisions [12] have been followed in the carrying on of this study. Approval to the study protocol has been granted by the Institutional Review Board (IRB) of Public Health Institution (PHI)-Psychiatric Hospital Demir Hisar in Demir Hisar and PHI-Psychiatric Hospital Negorci in Negorci, Gevegelija, North Macedonia, with the authorization signed on 15.06.2021 and 13.09.2021, respectively.

### 2.1. Participants

The study was conducted between May 2021 and October 2021 and included a patient group and a control group.

#### 2.1.1. Patient Group

Individuals who were treated at the Psychiatric Hospitals of Demir Hisar and Negorci, North Macedonia, with a clinician-confirmed diagnosis of bipolar disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [13], were enrolled in the study. Additional inclusion criteria were: age 18 or over 18 years old and having the capacity of providing informed consent. Exclusion criteria were: non-acceptance to participate in the study (non-signing the informed consent for accepting the participation in the study), patients with another psychiatric diagnosis and the age of the patients less than 18 years.

#### 2.1.2. Control Group

Healthy control subjects were included from the general population upon completion of patient recruitment. Inclusion criteria were: people without psychiatric diagnosis (the absence of symptoms indicating a psychiatric illness was verified by a negative medical history and by a medical interview), on the territory of the Republic of North Macedonia aged 18 or over 18 years old without gender exclusion, with previously signed informed consent. The absence of a personal history of any psychiatric disorder and the absence of a family history of psychiatric disorder in a first-degree relative was another criterium for inclusion in the study. Exclusion criteria were non-acceptance to participate in the study (non-signing the informed consent for accepting the participation in the study) and age less than 18 years. All included subjects provided written informed consent and were invited to fill in the Macedonian version of the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN).

### 2.2. Measures

A Macedonian version of the BRIAN has been prepared according to standard procedures [14]. The BRIAN was translated into the Macedonian language by a bilingual native editor, then back-translated into English by another bilingual native editor. The final version resulted from a consultation with a third independent researcher, who contributed to harmonizing the translation and back-translation of the BRIAN. The final version was also compared with the previously validated Italian version [9] by a bilingual researcher. The BRIAN includes 18 items and addresses the following dimensions: sleep, activities, social rhythms and eating patterns. The Macedonian version is included in the current paper as *Appendix A*.

### 2.3. Statistics

Data were imputed in Excel (*Appendix B*) and analyzed using the Statistical Package for Social Sciences (SPSS) version 27. All tests were two-tailed, with alpha set at  $p < 0.05$ . Means with standard deviation, or counts and percentages, were used to describe the distribution of the data in the sample. Unpaired t-test (after Levene correction for inequality of variance) or ANOVA, when appropriate, was used to determine whether continuous variables differed among groups of subjects. Chi-square tests were used for categorical data. Pearson correlation coefficient was used for correlations. Reliability was measured as internal coherence using Cronbach's alpha. For group comparisons, a rule of thumb assumes that reliability values of 0.70 are considered acceptable [15]. Criterion validity, intended as the degree to which the scores of the instrument were an adequate reflection of a "gold standard" [16], was assessed by comparing the scores of the BRIAN between patients and healthy controls. We expected patients reported higher scores than controls at medium effect size.

A priori power analysis was performed to calculate the minimum sample size to be enrolled to reach the expected effect size in the differences between patients and controls. We calculated that 50 participants per group would have been enough to observe a near medium effect (0.50) in Cohen's  $d$  (standardized mean difference) with alpha set at 0.05 and beta at 0.20 (power = 80%).

### 2.4. Receiver Operating Characteristics (ROC) Analysis Curve

We used the ROC curve to test the criterion validity of the tools. The degree to which the instrument's scores adequately reflected a "gold standard" was the goal of criterion validity [17]. For this study, we used the clinical diagnosis as a "gold standard" for reference and tested with the ROC curve analysis the capacity of the BRIAN in distinguishing between diagnostic groups. From the analysis, we extracted the following estimates: the sensitivity (the probability of identifying a patient with BD); the specificity (the probability of identifying a patient without BD); the positive predictive value (PPV: the probability that a person is a case of BD when a positive test result is observed); the negative predictive value (NPV: the probability that a person is not a case of BD when a negative test result is observed); and the positive diagnostic likelihood ratio (which is the odds ratio that a positive test will

be observed in a population of people with BD compared to the odds that the same result will be observed among a population of people without BD).

The area under the curve (AUC; with 95% confidence interval [CI]) was used to estimate the accuracy of the prediction. Agreed threshold for the AUC was:  $\leq .70$ , poor; between  $.70$  and  $.80$ , fair; between  $.80$  and  $.90$ , good; above  $.90$ , excellent [18]. We used the “pROC” package running in R to perform the ROC analysis [19], while the best cut-off point for the BRIAN was established according to the Youden (1950) [20] method with the “OptimalCutpoints” package [21].

**3. RESULTS**

No difference by gender or age was noticed (Table 1).

Patients differed from controls in education and occupation. These differences are expected because people with bipolar disorder, due to the nature of the disease, have obstacles and limitations in using their potential for higher education levels (university), and also are limited in the constancy in workplaces. Data violated normality for some of the BRIAN scales in patients (Kolmogorov-Smirnov with Lilliefors corrections ‘s p < 0.05 for Sociality and Rhythms subscales); data violated normality for all BRIAN scales in controls. However, the t-test is pretty robust to depart from the normality assumption.

Reliability, as measured with Cronbach’s alpha, was good in BD subjects, except for the Rhythms subscale; reliability in controls was less good, especially for the Sleep and Rhythms subscales (Table 2).

**Table 1. General characteristics of the participants included in the study.**

	People with Bipolar Disorder Diagnosis	People without Psychiatric Disorder Diagnosis	Descriptive Statistics
	N = 50	N = 50	
Gender	28 (56%)	21 (42%)	$\chi^2=1,961$ ; df=1; p=0.161;
Men	22 (44%)	29 (58%)	
Women			
Age	48.5±11.1	44.8±13.3	F[1;98]=2.36; p=0.128 HC vs BD by age category: $\chi^2=6.67$ ; df=1; p=0.154
Mean±Standard deviation	3 (6%)	10 (20%)	
21-30	8 (16%)	9 (18%)	
31-40	17 (34%)	11(22%)	
41-50	14 (28%)	9 (18%)	
51-60	8 (16%)	11 (22%)	
61-70			
Education	13 (26%)	4 (8%)	$\chi^2=9,441$ ; df=2; p=0.009;
Compulsory school or less	27 (54%)	24 (48%)	
High school or professional University degree or higher	10 (20%)	22 (44%)	
Civil status	18 (36%)	14 (28%)	$\chi^2=2,112$ ; df=3; p=0.549;
Single	22 (44%)	28 (56%)	
Married and cohabiting	8 (16%)	5 (10%)	
Divorced or separated	2 (4%)	3 (6%)	
Widowed			
Occupation	13 (26%)	4 (8%)	$\chi^2=13,187$ ; df=3; p=0.004;
Student or housewife	20 (40%)	12 (24%)	
Unemployed	16 (32%)	29 (58%)	
Employed	1 (2%)	5 (10%)	
Retired or disabled			
Phase	29 (58%)		
Depression	13 (26%)		
Mania or hypomania	5 (10%)	-	
Mix status	3 (6%)		
Euthymia			

Data were expressed as counts and percentages or as mean and standard deviation

**Table 2. Reliability statistics.**

Control Subjects		
Section	Cronbach's Alpha	Number of Items
Sleep	0.41	5 (1-5)
Activity	0.80	5 (6-10)
Sociality	0.57	4 (11-14)
Eating	0.78	4 (15-18)
Rhythm	-0.29	3 (19-21)

(Table 2) contd.....

Control Subjects		
Total score	0.77	21 (1-21)
Bipolar disorder subjects		
Section	Cronbach's Alpha	Number of Items
Sleep	0.72	5 (1-5)
Activity	0.92	5 (6-10)
Sociality	0.56	4 (11-14)
Eating	0.92	4 (15-18)
Rhythm	-0.14	3 (19-21)
Total score	0.88	21 (1-21)

Table 3. Scores on the five domains of the BRIAN.

Section	Control Group	Patient Group	P	T-test	dl
Sleep	9.82±2.18	15.06±3.09	0.00	9.78	88.09
Activity	7.78±2.69	14.12±4.37	0.00	8.71	81.51
Sociality	5.58±1.63	10.52±2.55	0.00	11.51	83.17
Eating	6.26±2.49	10.74±4.02	0.00	6.68	81.86
Rhythm	5.94±1.13	6.98±1.33	0.00	4.20	95.51
Total score	35.38±6.63	57.42±11.45	0.00	11.77	78.55

Values are presented in mean±standard deviations.

Furthermore, the tool was able to discriminate patient groups with controls, with large differences on all subscales (Table 3). However, since the reliability was suboptimal for some subscales, these differences cannot be entirely trusted.

The BRIAN distinguished people with high AUC (0.95; 95%CI: 0.91 – 0.99) diagnosed with BD from putatively healthy controls (Fig. 1). The best threshold for the dif-

ferentiation of BD subjects from controls was 46. Sensitivity and specificity at the best threshold were 86% and 96%. BRIAN showed a poorer NPV (87.3%) than its PPV (95.5%). The positive diagnostic likelihood ratio was high: 21.5. In the investigated samples, just 2 controls (4%), as against 43 patient groups (86%), scored at or above the cut-off on the BRIAN ( $\chi^2_{\text{Yates}}=64.6$ ;  $df=1$ ;  $p<0.0001$ ). The ROC analysis does not assume the normality distribution of the numerical variable.

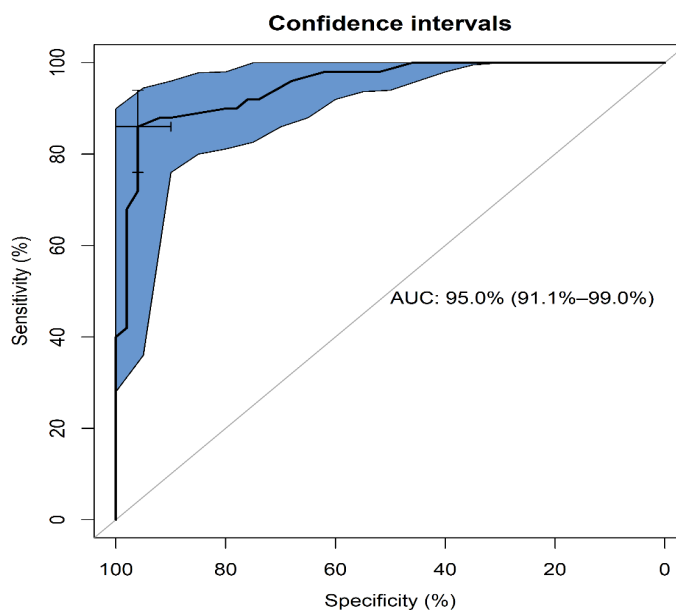


Fig. (1). ROC analysis curve of Macedonian version of BRIAN.

#### 4. DISCUSSION

We studied the validity and reliability of the Macedonia version of BRIAN, which has been used to measure biological rhythm in psychiatric backgrounds. In particular, individuals with BD, which is known to relate closely with circadian rhythm disturbances, were estimated with control subjects, and a remarkable intergroup difference was verified. The reliability of the Macedonian version of BRIAN, validated through this study, was similar to that determined in earlier studies of BRIAN [22, 23]. The Cronbach's alpha values for the entire scale and for each subscale were very good and additionally confirmed the good reliability of this tool. Otherwise, the traditional approach of measuring biological rhythm implies continuous measurement of the core body temperature; however, most studies measure behavioral and molecular circadian rhythms [24 - 26]. Molecular-level assessment may be the most precise; however, this method is invasive and is complex to apply to many subjects [27, 28].

A biological rhythm measurement based on the BRIAN scale is subject to recall bias and dependent on the reliability of answers [29, 30] but can be easily evaluated at any time; furthermore, the ability to assess 5 subdomains makes this scale an attractive clinical and research tool. This result can be interpreted in the context of previous studies, which reported a close relationship between biological rhythm disturbances and more frequent and severe depressive features in patients with BD. In the present study, the BRIAN score was importantly higher in people with BD than in normal control subjects. This is compatible with previous studies putting forward that individuals with BD show more disturbed biological rhythms as determined by the BRIAN [31 - 35]. Further investigation into the association between the prevalence and intensity of mood symptoms and the BRIAN will be required in the future. This finding contributes important confirmation concerning an approach established on biological rhythms in clinical practices and research of mood disorders. As the main reason for the significant difference in occupation between subjects with bipolar disorder and controls is the reduced ability for consistency and continuity in the workplace, which leads to the loss of the same and obtaining the status of an unemployed person. As well sleep rhythms are thought to depend on the occupation. Moreover, the human circadian rhythm cannot easily adapt to these fast shifts in bipolar disorder. Indeed, in inter-episode bipolar disorder, lower and more variable sleep efficiency and variability in falling asleep time are related to worse illness course and outcome [36]. Relative to the inter-episode phase, sleep disturbance escalates just before an episode, worsens during an episode and does not always resolve with medication [37, 38]

The potential application of this tool based on validity, as a screener, should also be addressed. From this point of view, the authors considered that a screener, in fact, can be convenient if it does not produce false positives and hence is efficient in producing a high predictive value. Actually, if the test is low-priced, noninvasive and adaptable, it can lead to a second evaluation only on positives with a more precise diagnostic tool. It is obvious that this study was conducted by comparing bipolar subjects to people without psychiatric diagnoses.

Practically, a screening tool should be able to distinguish, especially among people with various pathologies. From this perspective, it has to look deeper into the fact that the disturbances of biological rhythms have recently been revealed not only in bipolar disorder but as well in other psychiatric disorders such as schizophrenia, autism, major depression, stress related disorders [39 - 42]. Very interestingly, even on the level of genetic determinants, an association between dysregulation of biological rhythms and bipolar disorder has been observed [43].

The BRIAN showed to be able to distinguish patients diagnosed with BD from putatively healthy controls, with good accuracy (when measured with AUC) and a very good informative positive diagnostic likelihood ratio (around 21). On the basis of the PPV and the NPV, the BRIAN is a screener that is good at confirming the presence of a BD, although it can also contribute to excluding its presence.

Few studies applied the receiver operating characteristic curve (ROC) to the BRIAN to determine its screening capacity. In a study on 60 newly diagnosed Japanese patients with delayed sleep-wake phase disorder, a threshold of 40 on the BRIAN discriminated patients from controls with a sensitivity of 80.0% and a specificity of 75.6% [44]. Since the study was on a condition different from BD, we cannot compare the threshold we have found with the one of the Japanese studies. On the other hand, the study of validation of the Italian version of BRIAN showed good accuracy in screening between BD (44 subjects) and non-BD (38 subjects). It was noticed quite good performance in specificity, for example, at cutoff 16, with a sensitivity of 68.2% and excellent specificity of 92.5% [9].

#### 5. LIMITATIONS

The limited sample size and the preliminary nature of the data represent obvious limitations of the study, which was designed to validate the Macedonian version of the BRIAN, not to test its screening effects. Despite their preliminary nature, the reported findings purport an innovative approach in the development of screening tools aimed at detecting the consequences of the symptoms (on circadian rhythms) rather than simply counting their occurrence. As evidenced by past studies, the tool emerges as a very practical tool for evaluating the bipolar disorder phenotype because it focuses on biological rhythms, contrasting other scales that only indirectly consider biological rhythm by evaluating seasonality or chronotype. In the future, this version of the scale will probably be used for biological rhythm measurements in different psychiatric areas and for active research and clinical practice concerning mood disorders.

#### CONCLUSION

Due to the significance of monitoring biological rhythms with a relevant and consistent instrument, BRIAN can be an applicable tool both in research and clinical practice with bipolar patients. The study suggests that the Macedonian version of this instrument has acceptable psychometric characteristics and also encourages the chance of developing mixed screening tools by incorporating elements of biological rhythm dysregulation into the routine evaluation of mood.

**LIST OF ABBREVIATIONS**

**BRIAN** = Biological Rhythms Interview of Assessment in Neuropsychiatry  
**BD** = Bipolar Disorder

**AUTHORS' CONTRIBUTIONS**

GK has prepared the first draft; GK and AP prepared the statistical analysis, IB, PIK, AP, MGC revised it. All authors approved the final version of the paper.

**ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

Approval to the study protocol has been granted by the Institutional Review Board (IRB) of Public Health Institution (PHI)-Psychiatric Hospital Demir Hisar in Demir Hisar and PHI-Psychiatric Hospital Negorci in Negorci, Gevegelija, North Macedonia, with the authorization signed on 15.06.2021 and 13.09.2021, respectively.

**HUMAN AND ANIMAL RIGHTS**

No animals were used for studies that are the basis of this research. All the humans were used in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013 (<http://ethics.iit.edu/ecodes/node/3931>).

**CONSENT FOR PUBLICATION**

Informed consent was obtained from all participants of this study.

**STANDARDS OF REPORTING**

STROBE guidelines were followed.

**AVAILABILITY OF DATA AND MATERIALS**

The dataset that supports the results and findings of this research is available from the corresponding author [G.K.] upon reasonable request.

**FUNDING**

None.

**CONFLICT OF INTEREST**

The authors declare no conflicts of interest, financial or otherwise.

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