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Validation of the Italian Version of the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN): Some Considerations on its Screening Usefulness

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Abstract: Introduction: Abnormalities in biological rhythms (BR) may have a role in the pathophysiology of Bipolar Disorders (BD). The objective of this study is to validate the Italian version of the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN), a useful tool in studying BR, and measure its accuracy in discriminating BD. Methods: 44 outpatients with DSM-IV-TR diagnosis of BD and 38 controls balanced for sex and age were consecutively recruited. The discriminant validity of BRIAN for the screening of BD and its test re-test reliability in two evaluations were assessed. Results: BD patients scored 22.22±11.19 in BRIAN against 7.13±5.6 of the control group (P<0.0001). BRIAN showed a good accuracy to screen between BD non-BD at cutoff 16, a sensitivity was 68.2 and specificity was 92.5. The test-retest stability measured using Pearson's coefficient found very high r values for each section and the total score, thus indicating a correlation at the two times of statistical significance in all measures. Cohen's Kappa varied from 0.47 in the sociality section to 0.80 in the sleep section, with a total K mean of 0.65. Conclusion: The results show that the Italian version of BRIAN has good discriminant validity in detecting BD from healthy controls and shows good test-retest reliability. The study suggests the possibility of developing mixed screening tools by introducing items on dysregulation of biological rhythms to the usual measures of mood.

Keywords: Biological rhythms, bipolar disorders, BRIAN, Italian screening, validation.

1. INTRODUCTION

The course of bipolar disorder is, by definition, cyclical and characterized by episodes of depression and (hypo)mania with or without mixed features, with – or without - interepisodic euthymia [1]. As the mood switch involves a change of biological rhythms, with changes in sleeping patterns constituting perhaps the most relevant one, it was thought that abnormalities in biological rhythms might have a role in the pathophysiology of the disease [2]. From these considerations, the literature reports a relationship between biological rhythm disturbances and treatment and the onset, maintenance and remission of bipolar episodes [3]. There is also evidence about the relevance of dys-regulation of hormones and neurotransmitters that command biological rhythms in bipolar disorders [4-8]. Physiological and behavioral timekeeping processes are frequently found abnormal in bipolar disorders, thus a vulnerability to alterations in biological rhythms may play a certain role in the course of the disease [9]. Differences in the course of bipolar disorders may also be caused by genetic differences concerning regulation of biological rhythms [10]. Moreover, biological rhythm impairment has been associated with poor functioning and quality of life [11].

Thus, circadian rhythms are related to bipolar disorders in three different ways: (1) by considering its etiological/triggering role, (2) as a very reliable early warning sign of relapse, very useful in psychoeducation [12], and (3) its modification –by means of psychological or drug interventions - may have a therapeutic effect.

The Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) is an 18-items interviewer-administered instrument which aims to investigate four main areas related to circadian rhythm disturbance, namely: sleep, activities, social rhythms and eating patterns. Items are rated using a 4-point scale, (1)= no difficulty, (2)= mild difficulty, (3)= moderate difficulty, and (4) =severe difficulty. The BRIAN scores thus range from 1 to 72, where the higher scores suggest severe circadian rhythm disturbance [13]. To date, the scale is available in Portuguese, Spanish and English. Hereby we aim to validate the Italian version of this tool.

2. METHOD

2.1. Study Sample

44 euthymic (Young Mania Rating Scale (YMRS) <6, Hamilton Depression Rating Scales (HDRS) <8 for a period

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of at least one month before inclusion) outpatients with a DSM-IV-TR diagnosis of bipolar disorder and 38 control subjects balanced for sex and age were recruited. The comparison group was recruited from the general population within the catchment area of Cagliari, Italy. The test-retest reliability measure was carried out in half (N=41) of the sample recruited randomly out of the original sample after stratification by sex and diagnosis.

Diagnosis was conducted according to the "Advanced Neuropsychiatric Tools and Assessment Schedule" (ANTAS) [14] a semi-structured clinical interview derived in part from the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) non-patient version (SCID-I/NP) [15]. The control subjects were screened using the same interview to exclude current or lifetime psychiatric disorders. Controls had no first-degree relatives with bipolar disorder or other psychiatric disorders.

The study was approved by the Università Europea del Mediterraneo Onlus Ethics Committee and was carried out in compliance with the Helsinki Declaration of 1975 (the Evaluation, Support and Prevention Unit). All subjects contacted were informed about the study and when they decided to participate they signed a consensus form.

2.2. Assessment and Instruments

The clinical researchers were trained beforehand in the use of the study tools. One clinical researcher recorded the socio-demographic and clinical variables of each patient, administered the Italian version of the Young Mania Rating Scale (YMRS) [16], the 17-items Hamilton Depression Rating Scale (HDRS-17) [17] and the Global Assessment Functioning (GAF) scale [18] to confirm the stability of the patient's condition and overall functioning. She also recorded all the medication prescribed to the patient for each visit. Finally, a second researcher administered the BRIAN. Interviewers administering the BRIAN and the GAF, HDRS and YMRS were blinded to each other.

2.3. BRIAN

The BRIAN was developed by the Bipolar Disorders Program & INCT Translational Medicine and by the Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil. It is an interviewer-administered instrument designed for use by a trained clinician; the time frame studied refers to the last 14 days before assessment. The 18 items evaluating sleep, activities, social rhythm and eating patterns were probed for discriminant, content and construct validity. All items were rated using a 4-point scale scored 1 = not at all, 2 = seldom, 3 = sometimes, 4 =often, or in some items 1 =never, 2 = seldom, 3 = often, 4 =always. The global score was obtained when the scores of each item were added up. The score may be regrouped in five specific sections scoring sleep, activity, sociality, eating habits and rhythms.

The original version was translated into Italian to English, back translated and approved by two English native speakers working as researchers in the field of bipolar disorder.

A more detailed description of the instrument is shown in the original paper by Giglio *et al.* [12]. The Italian version is included in the current paper as an Appendix.

2.4. Psychometrics and Statistical Analysis

Statistical analysis was performed using SPSS for Windows – Version 11.0 (SPSS Inc., Chicago, IL, USA). The accuracy of the BRIAN score in discriminating between cases and controls (discriminant validity) was measured comparing mean BRIAN scores in the two groups with one-way ANOVA. Sensitivity and specificity of BRIAN at cutoff 20 was also carried out. The test re-test reliability of the BRIAN total score and the BRIAN sections (Sleep, Activity, Sociality, Eating, Rythms) was measured comparing to and t1 (1 week later) using both the correlation coefficient of Pearson and Cohen's kappa value.

3. RESULTS

44 bipolar patients (25 BD I, 19 BD II) and 38 healthy controls were included in the study (Table **1**). The mean age of the sample was 44.61 + 12.64 without differences between cases and controls regarding the distribution by sex.

The bipolar sample included 16 men (42.1%) and this rate was similar (16 men, 36.4%) in the control group. In the Bipolar Sample, 25 subjects were diagnosed as Bipolar I (30.5% of the whole sample) and 19 (23.3%) as Bipolar II (Table **1**).

Table 1. Characteristics of the sample and concurrent validity of the BRIAN.

Variable	Descrictive Statistics
N (%) sample	80 (100%)
Age (years) Bipolar (44) Not Bipolar (38)	mean $\pm$ sd = 44.61 $\pm$ 12.64 45.21 + 13.18 43.95±12.01 BP vs nBP F=0.20, df 1,80,81, P=0.604
Gender Male Female	 32 (39.0%) – 16 Bipolar Disorders (42.1%) 50 (61.0%) – 22 Bipolar Disorders (57.89%) BP vs nBP χ2=0.28, 1df, P=0.595
DSM-IV Diagnosis Bipolar Disorder I Bipolar Disorder II No Diagnosis	 25 (30.5%) 19 (23.2%) 38 (46.3%)
Brian Bipolar **Brian non Bipolar**	22.22±11.19 7.13±5.6 F=56.75, df 1,80,81, P<0.0001

Bipolar Patients scored 22.22±11.19 in BRIAN against 7.13±5.6 in the control group (F=56.75, df 1,80,81, P<0.0001). BRIAN showed good accuracy in screening between BD and non-BD with quite good performance in specificity, for example at cutoff 16, with a sensitivity of 68.2, specificity was excellent (92.5). Table **2** shows the performance of BRIAN as a screening tool for Bipolar Disorders at different cutoff points. Fig. (**1**) translates these results into a ROC Curve.

Table 2. Accuracy of BRIAN as screener for Bipolar Disorder.

Cutoff	Sensitivity	1-Specificity	Specificity	VPP	VPN
4	100	70	30	60	100
8	86.3	42.2	57.8	70.7	78.5
12	77.2	12.5	87.5	87.12	77.7
16	68.2	7.5	92.5	91.1	72.5
18	61.3	5.3	94.7	93.1	66.6
20	54.5	5.3	94.7	92.3	64.3
28	50	0	100	100	54.8

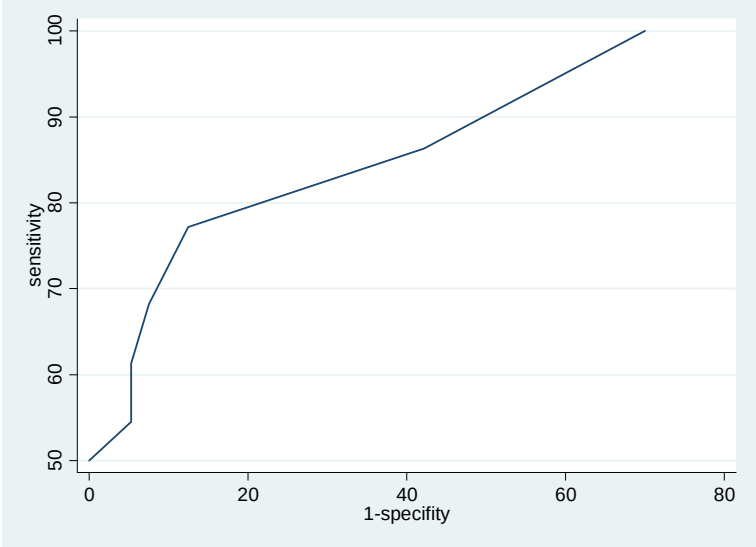

Fig. (1). ROC curve.

Table 3. Test-retest reliability of BRIAN.

Section	K (ES)	95% K	r Pearson (40df)	P	Mean t0	Mean t1	T -test
Sleep	0.80(0.13)	0.55-1.63	0.88	<0.0001	4.42±3.88	4.09±3.92	11.83
Activity	0.54 (0.18)	0.19-0.90	0.93	<0.0001	4.26±4.44	3.85±4.49	9.79
Sociality	0.47(0.19)	0.09-0.90	0.87	<0.0001	2.02±2.60	1.85±2.55	11.26
Eating	0.68(0.12)	0.45-0.91	0.85	<0.0001	2.42±2.87	1.85±2.23	10.23
Rhythm	0.76 (0.15)	0.45-1.07	0.35	0.045	2.40±1.24	2.57±1.15	1.72
Total Score	0.65 (0.13)	0.37-0.90	0.93	<0.0001	15.54±11.4	14.23±11.56	16.78

Test-retest stability was measured in half of the sample randomly recruited after stratification by diagnosis and sex (8 Male; age 44.83, 19 Bipolar). It was found by using both the correlation coefficient of Pearson and Cohen's kappa value. Table **2** shows the K values (with standard error) and the r values. The Pearson r values were found very high in each section and in the total score, thus indicating a correlation between the two scores with statistical significance in all measures. The K value varied from 0.47 in the sociality section to 0.80 in the sleep section. The K of the total BRIAN Score was 0.65.

DISCUSSION

The Italian version of the BRIAN is a valid and reliable tool with psychometric properties equivalent to the original tool and has a good test-retest reliability measured with K statistics.

Moreover, the results of the present study suggest that the Italian version of the BRIAN shows an interesting discriminant validity in screening for bipolar disorder. The high discriminant validity allows the obtaining of an excellent performance using the BRIAN as a screening tool at the cutoff of 20. From this perspective, we must consider that a screener can really be useful if it does not generate false positives and thus is capable of producing a high predictive value of a negative. In fact, if the test is inexpensive, noninvasive and easy to apply, it can lead to a second evaluation only on positives with a more accurate diagnostic tool, or if another screener is available, one that is equally inexpensive and easy to apply but with complementary performance (with high sensitivity and low specificity), they can be administered simultaneously. We must therefore take into account that the predictive value of negative evidence we found at a cutoff of 20 is noteworthy. It is to be underscored that the BRIAN was not conceived or initially tested as a screening tool, but even then it showed acceptable screening properties.

The results are of interest because of the well-known difficulties in research in developing accurate screeners for bipolar disorder due to the several existing biases which include memory biases, perception of hypomania as a non-pathological state and others [1]. In particular, current screening tools show good sensitivity but low specificity. From this point of view the BRIAN could be highly complementary to questionnaires such as the Mood Disorder Questionnaire (MDQ) and Hypomania Checklist-32 (HCL-32) and its use associated with a clinical questionnaire (more sensitive but less specific) could make the screening very effective.

In all cases the result was so good as to suggest extending the possibility of using a scale of biological rhythms as screening for bipolar disorder or introducing some items on biological rhythms into well-known clinical screeners such as the MDQ [19] or HCL-32 [20].

From this point of view we must consider that this study was conducted by comparing patients with bipolar disorder to people without psychiatric diagnoses. In practice, a screening tool should be able to discriminate especially among people with different pathologies. From this perspective it must be considered that the disturbances of biological rhythms have recently been reported not only in bipolar disorders but also in other psychiatric disorders such as major depression, stress related disorders, autism and schizophrenia [21-24]. However, it has been highlighted in recent literature that the weight of the dysregulation of biological rhythms in bipolar disorder is higher than in other disorders and can be described as a kind of characteristic of these disorders [25, 26]. Even on the level of genetic determinants a justification for the association between dysregulation of biological rhythms and bipolar syndromes has been found [27]. If it is thus evident that the screening of biological rhythm dysregulation can divide people with bipolar disorder from people without a psychiatric diagnosis, it follows that this can occur during a screening of the general population.

However, the extent of biological rhythm dysregulation has never been introduced as a possible screening tool at the speculative level. In the light of these psychometric results it would be interesting to design a tool that that combines the features of mixed measurement of hyperactivity and hyperergia typical of most known screens, such as the MDQ and HCL, with the measurement of biological rhythms. Test-retest reliability probably adds some new data to the first validation study. The study indicates that the total BRIAN score and the BRIAN sub-section scores reach a good correlation in the two measures (t0 and t1) measured by means of Pearson's correlation factor. The test re-test reliability for each section showed a K agreement from sufficient to good. Sufficient (K from 0.40 to 0.60) was shown for Sociality and Activity sections; Good (K from 0.60 to 0.80) was shown for Sleep, Eating, Rhythm sections and total score.

The study of the regulation of biological rhythms is becoming increasingly important in the field of bipolar disorders. The circadian time keeping process is responsible for controlling sleep patterns. The role of Melatonin secretion in this control is well-known and is today the objective of several studies that may contribute to better understanding the physiopathological process of bipolar disorders as the genetic component and may suggest newer therapeutic pathways [8]. Bipolar subjects, regardless of the mood state, experience a wide variety of disruptions of biological rhythms and sleep disorders [19]. A decreasing amount of deep sleep per night comes just before the onset of a manic episode and may come before a depressive episode [28]. Therefore, the decrease in sleep has been identified as a predictor of manic episodes [28]. Psychoeducational programs have shown that preventing disruptions in the circadian sleep cycle is important in maintaining a regular sleep schedule [11].

LIMITATION

Amongst the limitations we must consider the preliminary nature of the data, the limited sample size and the fact that the current study was designed to validate the Italian version of the BRIAN, not to test its screening properties. Screening performances need to be measured in target populations of future screening studies (ie: community samples), and/or clinical samples including euthymic patients with major depressive disorder because a differential diagnosis between bipolar depression and unipolar depression is often the most important issue in this area in clinical practice. The results must be considered an innovative preliminary report suggesting a new perspective in the development of screening tools, it can be complementary to those explored so far.

CONCLUSION

Due to the relevance of monitoring biological rhythms with a valuable and reproducible instrument, BRIAN can be a useful tool both in research and clinical practice with bipolar patients. The Italian version was shown to have good psychometric proprieties. The results also show that BRIAN has good discriminant validity in detecting BD from healthy controls and shows good test-retest reliability. The study suggests the possibility of developing mixed screening tools by introducing items on biological rhythm dysregulation into the usual measures of mood

AUTHOR'S CONTRIBUTIONS

MGC and FC participated in the design of the study, in the analysis of the data and drafted the manuscript. MFM,

EP, MP and RM participated in acquisition of data and critical revision of the manuscript. FK and EV participated in the analysis of the data and drafted the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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