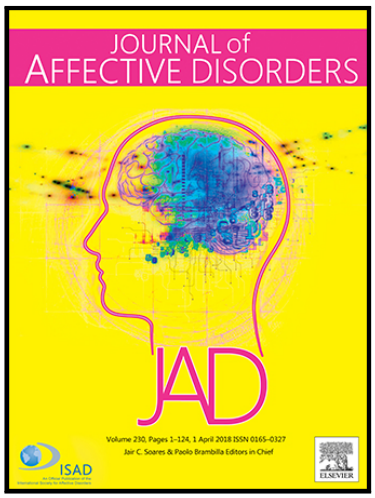

Non-linear analysis of the Heart Rate Variability in characterization of manic and euthymic phases of Bipolar Disorder

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Highlights:

- This is the first study that highlights the sympathetic predominance during mania using non-linear HRV assessment tools such as Recurrence Plots and Symbolic Analyzes, proving clinical improvement after treatment.

Non-linear analysis of the Heart Rate Variability in characterization of manic and euthymic phases of Bipolar Disorder

Running Title: Bipolar Disorder and Autonomic Impairment

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Abstract

Background ς Bipolar Disorder (BD) has been associated with autonomic nervous system (ANS) dysregulation, with a consequent increase in mortality. Recent work highlights the non-linear analysis of ANS function. Our objective was to compare ANS modulation using recurrence plots (RP) and symbolic analysis (SA) in manic and euthymic phases of BD to controls. Methods ς Eighteen male patients (33.1±12.0 years) were assessed during mania and at discharge in the euthymic phase compared and to a healthy group matched by age (33.9±10.8 years). Electrocardiographic series (1,000 RR intervals, at rest, in supine position) were captured using Polar Advantage RS800CX equipment and Heart Rate Variability (HRV) ǿl·ă l·yΊ·fèăŜŘ dzăλyƎ wt l·yŘ {!Φ {űl·űλăűλŎl·f l·yΊ·fèăλă ǿl·ă ǇŜ₪ƵǊΥŜŘ dzăλyƎ !bh±! ǿλűK ¢dzʅŜèΩă post-test. The threshold for statistical significance was set at P ғ лΦлр l·yŘ /ƵKŜyΩă *d* effect size was also quantified considering *d* > 0.8 as an important effect. The study was registered into the Clinical Trials Registration (ClinicalTrials.gov: NCT01272518). Results: Manic group presented significantly higher linearity before treatment (P<0.05) compared to controls considering RP variables. Cohen's d values had a large effect size ranging from 0.888 to 1.227. In the manic phase, SA showed predominance of the sympathetic component (OV%) with reduction of the parasympathetic component (2LV% and 2UV%) with reversion post treatment including higher Shannon Entropy (SE) indicating higher complexity. Limitations - short follow-up (1 month) and small number of patients. Conclusions - Non-linear analyzes may be used as supplementary tools for understanding autonomic function in BD during mania and after drug treatment.

Keywords: Recurrence Plots; Symbolic Analysis; Bipolar Disorder; Autonomic Nervous System; Heart Rate Variability; Nonlinear Domain.

1. INTRODUCTION

Autonomic Nervous System (ANS) dysregulation has been associated with bipolar disorder (BD) and others mental conditions[1,2] and to the risk of cardiovascular diseases[3-6]. Data on mortality related to cardiovascular diseases in bipolar patients have been reported since the beginning of the 20th century[7] ς perhaps due to autonomic imbalance[8], and seems to occur earlier compared to general population[9,10]. Contemporary clinical studies continue to demonstrate such association[8,11,12] with high prevalence of risk factors for cardiovascular disease including diabetes mellitus, hypertension and obesity[12-14].

This autonomic dysregulation can be evaluated by heart rate variability (HRV)[15], a measure that provides information relating to complex heartbeat dynamics that has important implications for psychophysiological and pathological states[5]. HRV can be used as an ANS integrity index for emotional states[16], where individuals with lower HRV have impaired emotional regulation[17], reflecting a feedback process between cortical, subcortical and cerebral trunk structures that regulate autonomic activity and human behavior[18], linking HRV and brain networks[17].

Several authors have demonstrated autonomic dysfunction and central autonomic network disturbances in BD[19,20], with reduced HRV a notable finding[2,21-23]. Linear analysis, both in time and in the frequency domain, have been commonly used[2,21-23]. However, nonlinear domain measures of HRV have also been studied[24,25] and are based on the complex systems theory[25]. The analysis of nonlinear data may provide greater accuracy in clinical diagnosis[25,26].

The methods of recurrence analysis by means of recurrence plots (RP), a visual representation of a given time-series data, have been used successfully in different areas[27-30]. Recurrence quantification analysis (RQA) is currently considered an important method for non-linear data analysis of several complex systems[31] and quantifies the number and duration of recurrences of a dynamical system presented by its space trajectory through the analysis of line inspection patterns[30]. This method has been shown to be useful in the diagnostic and prognostic evaluation in health and disease conditions and in the different age ranges[26]. Another method of non-linear HRV analysis is symbolic analysis (SA). This is a methodology that symbolizes the temporal course of one or more of the variables that describe the behavior of the dynamic system to study the complexity of this dynamic system as well as to evaluate the interactions between its parts[32,33]. It is emphasized that, a previous study in human being using cardiac pharmacological blockades established the cardiac autonomic representation of the symbols[34]. Thus, there has been interest in assessing nonlinear methods of HRV analysis to characterize autonomic cardiac function[35] as nonlinear analyses are good predictors of cardiac dysfunction[36] compared to time and frequency domain analyses, and also because they sufficiently characterize the complex dynamics of heartbeat generation since the mechanisms involved in cardiovascular regulation interact with each other in a nonlinear way[25].

Some non-linear methods focus mainly on the aspect of uncertainty, also understood as complexity, considering that the greater the uncertainty of a system, the greater its complexity or entropy. Translating to the physiological aspect, if an individual has good HRV, there will be greater uncertainty (or irregularity, or complexity) between the RR intervals and therefore it will be an indication of good homeostasis, the reverse occurring with sick individuals because the intervals will be much more regular and therefore less uncertainty (less entropy) in the system[25,32,33]. It is recognized that time and frequency domain variables do not assess the complexity of the systems. In addition, not all nonlinear variables measure complexity (or entropy). This was the justification for this work to have used variables that relate to non-linearity and variables that are strictly associated with complexity or uncertainty (Shannon entropy; SE)[25,32,33].

To our knowledge, this would be the first study to simultaneously use RP and SA to assess autonomic behavior in patients with BD before and after treatment, potentially allowing the detection of the effective individual contribution of each autonomic component. This study aimed to prospectively evaluate patients in the manic phase of BD considering changes in clinical status and its autonomic complex alterations, verifying the existence of changes with reversal to euthymia after treatment, as well as to compare BD patients with healthy individuals of the same age, using RP and Symbolic Analysis (SA).

2. METHODS

Eighteen male patients (age: 33.1±12.0 yo) in the manic phase of BD and hospitalized were accompanied from the time of admission until discharge over a period of approximately 1 month. All participants underwent a diagnostic assessment by a psychiatrist member of this study group (GLLW), based on the Mini International Neuropsychiatric Interview (MINI) Brazilian version 5.0 - DSM IV[37] on admission, as well as the Portuguese-validated version of the Bech-Rafaelsen Mania Scale (BR-MaS)[38] and in accordance with recommendations designed by Guidelines for Reporting Articles on Psychiatry and Heart Rate Variability (GRAPH) de Quintana et al.[39]

BD participants were excluded if they presented with any associated neurological condition or had already received prior electroconvulsive therapy; had a prior history of cardiovascular or metabolic disease or associated medications; had a prior history of drug use; displayed psychomotor agitation not allowing resting HRV recordings. Exclusion criteria were determined during an intensive clinical interview with one of the authors (GLLW). All patients underwent a 1-week wash-out period, and soon aripiprazole in combination with lithium was introduced for the treatment of the manic phase. Patients were on no additional medications. The first HRV measurement took place six days following the introduction of the drug combination, and the second measurement occurred on the day of discharge, when the same drugs were still in use. We considered the baseline measurement of HVR (first measurement) after the first 6

days that is when the serum lithium, in general, reaches the pharmacokinetic state of equilibrium, although still without clinical response[40].

Mean dosages of aripiprazole and lithium were 15.0±5.8 mg and 900.0± 283.8 mg, respectively. The mean serum lithium concentration was 0.85±0.13 mmol/L.

Eighteen healthy male individuals (age: 33.9±10.8 years old) comprised the control group. The study was approved by the local ethics committee (n° 459/2010), written inform consent was obtained, and the study was registered at Clinical.Trials.gov (identifier NCT01272518).

2.1. HRV Analysis

HRV recording is in accordance with standardization checklist of procedures by Catai et al.[41] and by specific guidelines of Quintana et al.[39]. Data was collected between the hours of 11:00 am and 01:00 pm, while participants were spontaneously breathing in a resting dorsal decubitus position for 20 minutes. RR intervals were measured with the Polar RS 800 CX (Polar, Kempele, Finland) using a heart rate chest strap monitor placed over the distal third of the sternum from which data was transmitted to a wrist sensor. The signals were captured with this equipment in units of time fixed at 1ms and the samples of RR intervals were collected at a frequency of 1000 Hz. This methodology has been validated in relation to Holter system and has demonstrated to provide accurate and reliable data[42]. All subjects in the control group followed the same methodology for HRV assessment[41]. We selected 1,000 RRi for HRV non-linear analysis, following the recommendations of Voss et al 2006[43], which suggests that this approach should be used with short-term recordings approximately 20 min[43].

2.2. Linear analysis

The RRi mean and standard deviation (STD) were calculated[15]. Spectral analysis was performed by the Fast Fourier Transform and analysed in low (LF: 0.04-0.15 Hz) and high frequency (HF: 0.15-0.50 Hz). Data was presented in absolute units (LFabs and HFabs) and in normalized units (LFnu and HFnu). The normalization consisted of dividing the LF power by the total power minus the power below 0.04 Hz, multiplying the ratio by 100[15]. The LFnu represents sympathetic cardiac modulation. The HF component is an indicator of vagal cardiac modulation[15].

2.3. Analysis of Recurrence Plots

Recurrence plots were constructed with the following parameters: dimension=2, time delay=2, ratio=70, line=2 and Volcano scheme, using Visual Recurrence Analysis 5.01 software

(http://visual-recurrence-analysis.software. informer.com; Eugene Kononov), which aids researchers in qualitative and qualitative analysis of Recurrence Plots.

The recurrence quantification analysis (RQA) measures the recurrence point density, diagonal and vertical line structures of the RP, identifying and quantifying the transitions between periodic, laminar, and chaotic states[26,28,30]. The analyzed quantitative variables were mean RR (mean of RR Intervals), Standard Deviation of the average of normal RR intervals (SDNN), Recurrence Rate (REC% - the percentage of recurrence points in an RP, corresponding to the correlation sum), Determinism (DET% - the percentage of recurrence points forming diagonal lines), Laminarity (LAM - the percentage of recurrence points forming vertical lines), Trapping Time (TT - the average length of the vertical lines), Shannon Entropy (SE - measures the complexity of the system) and Longest Diagonal Line (Lmax)[26,28,30].

2.4. Symbolic Analysis

The HRV symbolic analysis, described by Porta et al.[32,43,44], is based on the RRi transformation into a sequence of symbols, from the classification of the RRi in six levels (0 to 5). The sequence of symbols gives rise to the patterns (sequence of 3 symbols). All possible patterns were grouped, without losses, in 4 families, according to the number and type of variations between subsequent symbols: 1) 0V: pattern without variation (3 equal symbols), 2) 1V: with one variation (2 identical symbols and one different), 3) 2LV: pattern with 2 equal variations (the 3 symbols form an ascending or descending ramp) and 4) 2UV: pattern with 2 different variations (the 3 symbols form a peak or a valley). The occurrence rates of these families were calculated (0V%, 1V%, 2LV% and 2UV%).

Guzetti et al.[34] have shown that the 0V% index represents sympathetic cardiac autonomic modulation, the indexes 1V% and 2LV% represent the sympathetic and parasympathetic cardiac modulation, and 2UV% represents the parasympathetic cardiac modulation[32,41]. In this same way, the HRV complexity analysis was performed using the Shannon entropy (SE). This analysis measures the complexity of distribution of the patterns (sequences of three symbols) obtained in the time series RRi selected[32,44]. The index is high if the distribution is flat (all patterns are equally distributed and the series carries the maximum information), while the index is low if some patterns are more likely, others missing or absent[32,44].

2.5. Data analysis

For analysis of intervals between heart beats it is necessary to remove artifacts, impulses not initiated by the sinoatrial node and interferences. Noise effects were appropriately filtered according to T-RR Filter 1.1 beta[45]. The used filtering algorithm removes the RR intervals shorter than 350 ms, that are equivalent to the absolute or relative refractory periods and also

because such intervals may represent an increase in the heart rate which is incompatible with the normal sinus rhythm. This step also removes RR intervals longer than 1,200 ms. Comparing with the conventional filtering methods, which requires an expert to manually remove ectopic beats in the processing of HRV time series, this software allows that HRV analysis can be efficiently and quickly performed using an automatic adaptive filtering method[45].

Statistical analysis was performed with commercially available software (StatsDirect version 1,9,15 ς 2002). For comparative analysis between the three groups (euthymia, mania and controls) One-Way Analysis of Variance was used, applying the F test (variance ratio). In the case of P values less than or equal to 0.05, the post test of multiple comparisons of Tukey was used. The values for Bech-Rafaelsen Mania Scale (BR-MaS)[38] applied to assess the severity and evolution of the manic episode in the studied patients were presented as median and range because they are generated as an ordinal qualitative scale[1] (range: 0 ς 7) and were compared between mania and euthymic groups using the Wilcoxon's signed ranks test. Ordinal qualitative variable does not allow averaging since they are not true numbers. Descriptives results were expressed as mean ± SD or median (range) as adequate. The association between the changes in the HRV indices in RP and changes in the symbolic analysis was assessed by {LJŜI·ℕY˙I·yℚă Ŏ2ℕℕŜfI·ůλ2y˙Ŏ2ŜŦŦλŎλŜyΰΦ A P-valdzŜ ғ лΦлp ǿI·ă Ŏ2yΰăλŘŜℕŜŘ I·ă ăλΞyΛŦλŎI·yΰΣ I·yŘ /2KŜyℚă *d* effect size measures were determined for all pair-ǿλăŜ Ŏ2˙Y˙LJI·ℕλà2yΰă /2KŜyℚă *d* effect size[46] was also quantified considering *d* > 0.8 as an important effect.

3. 3 RESULTS

The Bech-Rafaelsen Mania Scale (BR-MaS) applied to assess the severity and evolution of the manic episode in the studied patients showed at admission a median of 19.8 (range: 12 ï 39) and at discharge a median of 1.10 (range: 0 ï 7) (P<0.0001; Wilcoxon's signed ranks test).

Recurrence quantification analysis (RQA) results show quantitative differences and also expressive differences in visual patterns of recurrence plots between controls and patients. The visualization of each group highlights the more geometric and repetitive aspect of the manic state in contrast to a more diffuse and uniform distribution in the control group, while the euthymic group presents as intermediate between the control group and the patient group at baseline. These observations provide evidence of the occurrence of physiological changes in BD, which justifies the use of the analysis of recurrence in the diagnostic and therapeutic arsenal for this disorder (Figure 1; Table 1)

Calculations of Cohen's d values[46] for quantification of effect size on the six studied variables in the recurrence plot (REC%, DET%, LAM, TT, Entropy and Max Line) indicated large effects, ranging from 0.888 to 1.227 (Table 2).

It was also observed that the recurrence measures obtained from the recurrence quantification analysis (RQA) of the post-treatment group clearly approached the values of the control group. An objective assessment of this fact is that of the nine variables studied, seven were significantly different in the comparison between mania and euthymia, while for the same nine variables, only one was significantly different in the comparison between euthymia and control.

Table 1 also presented the indices of SA and SE of the studied groups. The Mania phase was statistically different from Control and Euthymia. The mania phase had higher value of 0V%, representative of sympathetic modulation, lower values of 1V% and 2LV% (double modulation) and lower value of 2UV%, representative of the parasympathetic modulation. The SE was different in the mania phase when compared to Euthymia, where the mania presented lower values.

Table 3 presented the results from linear analysis. The RRi mean was different when comparing the studied 3 groups. Controls showed the highest values and mania the lowest. For STD, control was greater when compared to mania and euthymia. The spectral analysis shows: LFabs was higher in control subjects when compared to mania and euthymia patients. The LFnu, representative of cardiac sympathetic modulation, was higher in mania compared to euthymia. The HFabs was higher in control compared to mania and in the normalized units (HFnu), mania showed lower values compared to euthymia. These findings agree with the data of the symbolic analysis.

Table 4 shows the correlations obtained between the variables of the symbolic dynamics and the variables of the RP. Positive correlation between RP indexes and OV% was highlighted, suggesting an association between linearity and sympathetic modulation. On the other hand, the negative correlation between RP indexes and 2UV% is clear.

4. 4. DISCUSSION

The main findings of this study are follows: 1) Patients with BD have alterations in the nonlinear HRV dynamics consistent with high sympathetic heart modulation, reduced vagal modulation and lower complexity of HRV, compared to healthy individuals; 2) After treatment, it was possible to observe reduction of sympathetic modulation and increase of vagal (parasympathetic) modulation as well as increase of complexity, with no difference from controls, demonstrating improvement of the nonlinear HRV dynamics and treatment of the disease; 3) RP indexes correlated with symbolic indexes, making it possible to improve the interpretation of BD cardiac autonomic modulation; 4) RP and SA: were able to clearly show the clinical transition from mania to euthymia in patients with BD.

In recent years, systematic reviews and meta-analysis aimed at addressing the HRV responses in BD have been published[47-49], where there were no reports of studies that used Analysis of Recurrence Plots and only one study, described by Torre-Luque et al.[48], used symbolic dynamics for HRV analysis, but it was used to assess motor activity in mania, bipolar depression and healthy controls[50]. Therefore, our study adds in the literature, results from bipolar disorder in mania and euthymia using non-linear analysis little explored so far.

The HRV in BD has been evaluated in resting supine[23,24,26] and other conditions such as sleep[51] and at rest while sitting[52]. Although the difference in assessment condition, the results are consistent with studies at rest, where there is a decrease in HRV assessed by several methods. The study by Migliorini et al.[51] evaluated HRV (time and frequency domain, sample entropy, Lampel-ziv complexity, DFA, 1/f slope) and concluded that HRV is reduced in depression and bipolar disorder. The study of Henry et al.[52] was performed in sitting position in manic BD patients and schizophrenia. They performed several analyses (HR, SDNN, RMSSD, pNN50, spectral analysis and dynamic entropy and concluded that individuals with manic BD demonstrated a decrease in HRV as assessed by several measures.

Considering the ANS in the control of cardiovascular activity, and the possibility that its dysregulation precedes the beginning of major mood disorders[22], some authors correlate autonomic dysfunction with psychiatric symptoms[23,53,54], showing that the loss of vagal modulation is not restricted to the cardiac system. The present work showed the existence of autonomic dysfunction of the different branches of the ANS in patients with BD, a psychiatric disease with disorders of the central autonomic network[20], where reduction of HRV was also reported[22,23], with predominance of sympathetic modulation during mania and autonomic remodeling after treatment, with predominance of vagal modulation.

Most of the studies suggest that the predictive model of mental illness based only on standard diagnostic assessments is not adequate for the accuracy and replicability of the diagnosis and that other models of analysis considering the dynamic characteristics of these disorders would present greater predictability of which patients would change from one clinical state to another[54].

Valenza et al.[55] reported that heartbeat nonlinear dynamics are able to predict mood changes in BP. In our present work, the RP and Symbolic Analysis, nonlinear model of complex system analysis, were able to clearly show the clinical transition from mania to euthymia in patients with BD (Table 1 and 3), showing the cardiac autonomic modulation is significantly altered in untreated patients, allowing a non-invasive way of observing ANS changes after treatment.

One of the relevant aspects of SA is that this method allows to specifically differentiate the sympathetic component (0V%) from the parasympathetic component (2V%)[32,34] and thus allow the correlation with RP variables regarding this differentiation. In our study, for SA, it was observed that in the mania there was a predominance of the sympathetic component (OV%) and a reduction of the parasympathetic component (2LV% and 2UV%) (Table 3). We can then infer that 0V% increase is associated with less variability or greater recurrence of the elements of the system.

To our knowledge, this is the first time that were studied RP and SA simultaneously in BD and that was possible to make correlations and pathophysiological associations with symbolic analysis, in terms of sympathetic and parasympathetic functioning.

In our present study, in relation to the state of mania, when using RP, we could observe a higher REC% and higher SE, indicating a higher linearity and lower homeostasis. In this analysis, the SE is related to determinism and measures the complexity of the diagonals, showing higher values during mania, clearly indicating less complexity of the system and, therefore, greater linearity. This can be confirmed after treatment, where there was improvement of the cardiac ANS and the patients in the euthymia presented no difference in relation to the controls. These observations provide evidence of the occurrence of physiological changes in BD, which justifies the use of the analysis of recurrence in the diagnostic and therapeutic arsenal for this disorder.

There is a clear difference between the interpretation of SE values using RP or SA. This difference is due to the fact that, in the symbolic analysis, the SE is a measure of the complexity of the possible "words" of the system and, the greater the number of words, the greater the variability and therefore the greater complexity, indicating better physiological conditions but, in the recurrence graph, SE is a measure of the complexity of the "diagonals" present in the system and since diagonals represent determinism, the higher the SE value, the greater the system determinism, indicating greater linearity and lower homeostasis of the organism[25].

Patients diagnosed with serious mental disorders may die earlier than the general population, reducing life expectancy[56,57]. BD has one of the highest suicide risks[57,58], but also cardiovascular disease is one of the main cause of mortality[8,12]. The early and definitive diagnosis of mood disorders is important and, currently, the focus of the main scientific research in this area. Thus, the novelty of this study was correlating the RQA and SA variables with the sympathetic and parasympathetic functioning in BD. This noninvasive, simple, and a cost-effective analysis allows to monitor cardiovascular parameters before and after treatment compared to healthy individuals and to observe autonomic alteration in advance and thus enable to treat the patient before the symptoms of the disease reappear.

Voss et al.[43] discussed about the Emotional Motor System (EMS) as a separate motor system that acts independently from the primary somatic motor system, with influences somatic ăèăúŜϒ ʤzyŘŜℕ fΛϒōλǑ Ǒ2yύℕ2f℗ {2ϒŜ 9a{ ófI·ύŜℕI·f LJI·ℕŭú ăúℕʤzǑŭʤzℕŠă I·ℕŜ ℕŜfI·ύŜŘ ű2 ăLJŜǑλŬǑ emotional reactions whereas the neurotransmitters systems (norepinephrine, serotonine, acetylcholine and dopamine) have an important role in the EMS medial part. Considering the cardiovascular functioning, cortical areas (mostly located in the frontal cortex) seem to be involved in both perception and the motor control and the overlap of the neurotransmitters I·yŘ ăLJŜǑλŬǑ ōℕI·λyϒI·ℕŜI·ă λyØ2fØŜŘ λyϒúKŜ autonomic function and in the pathophysiology of some brain disorders would justify an autonomic dysfunction in BD.

Studies on HRV has reported a variety of behaviors including positive mood states, emotional regulation, cognitive function, inflammatory processes and brain plasticity. Research considering HRV changes and the neurophysiology BD are rare, especially in the manic phase. Vagal dysfunction relates to poor homeostatic behavior and to

increased morbidity and mortality[3-5]. Accordingly, to Martinez-Aran et al.[59], patients with BD have deficits in executive control, learning and verbal memory, working memory and sustained attention, especially during manic phase, where neurotoxic pathophysiological changes (reduced brain-derived neurotrophic factor (BNDF) and increased inflammatory cytokines) are observed. Kemp et al.[4,5,60] reported that HRV changes caused by the vagus nerve leading to normalized function indirectly stimulate neurogenesis through the expression of BNDF, with consequent cognitive improvement. Kemp et al.[4] highlighted that another important mechanism to be considered, that is the association between vagal activity and social cognition, where low HRV may indicate difficulty in maintaining social relationships and emotional processing, especially during a manic phase[61].

The literature has given special emphasis to the use of non-linear methods in the assessment of autonomic behavior in mood disorders. Voss et al.[43] revised the principal methods of time-domain, frequency- domain, and nonlinear analyses of HRV, blood pressure variability, as well as methods for coupling and interaction analyses. In the study, the authors highlight especially the non-linear domain for the use of Detrended Fluctuation Analysis (DFA), Approximate Entropy (ApEn) and Symbolic Analysis (SA). The SA, as previously mentioned, allows a simplified description of the dynamics of a system with a limited amount of symbols. Voss et al.[43] concluded their study stating that prospective studies of cardiovascular changes in mania and depression are needed to evaluate a psychopathological state in connection with cardiovascular changes and that these studies should consider the application of nonlinear methods, and a multivariate approach in addition to the traditional analysis of HRV.

Todder et al.[62] studied 32 euthymic bipolar patients and 24 controls both during complete rest. Nonlinear analysis (Poincare plot, largest Lyapunov exponent, minimal embedding dimension and symbolic dynamic) was used. They concluded that the nonlinear analysis of HRV ŘłŘyŰú support the notation that there is a disturbance in the autonomic nervous system of BD patients in the euthymic state. Based on the results of our study, this conclusion is not completely right. We have demonstrated that actually there was no significant difference between euthymia and controls but the differences were quite evident between mania and euthymia showing that there is an evident disturbance in the autonomic nervous system of bipolar patients in the mania state, which can be reversed with the use of specific drugs.

Valenza et al.[55] also studied mood changes in BD and exclusively through heart beat nonlinear dynamics. They studied 14 bipolar spectrum patients (age: 33.43 ± 9.76, age range: 23ς54; six females). Each patient was monitored twice a week, for 14 weeks, being able to perform normal unstructured activities. Relatively to the nonlinear variables they studied more specifically, sample entropy (SampEn), Approximate entropy (ApEn), features from the recurrence plot by means of the recurrence quantification analysis (RQA), and the detrended fluctuation analysis (DFA). They were able to obtain personalized prediction accuracies in forecasting a mood state of 69% on average, reaching values as high as 83.3%. They concluded that this approach opens to the possibility of predicting mood states in bipolar patients through heartbeat nonlinear dynamics exclusively.

Our results are in accordance with the available literature and so we concluded that these non-linear analyses RP and SA provide important and complementary tools for the study of the evolution and prognosis of diseases with autonomic involvement as demonstrated in this study with BD, where drug treatment reestablished the autonomic functioning raising HRV values of manic patients to levels closer to that observed in control individuals in the euthymic phase.

4.1. Limitations

Although we were able to show patients' autonomic and clinical improvement after treatment, this study has some few limitations as the short follow-up (1 month) and small number of patients. Also, a convenience sample was used, characterized by all cases that sought the hospital for treatment and that met the inclusion criteria. The finding of significant statistical differences between the groups, in itself, validates the sample size used. Despite this, the sampling power was calculated *a posteriori*, based on the results of the symbolic analysis, indicating a power always greater than 95%.

Author Statement

Michele Lima Gregório: HRV analyse, statistical analyse, final manuscript preparation.

Guilherme Luiz Lopes Wazen: patient selection and treatment, HRV registration.

Andrew Haddon Kemp: final manuscript reading and correction.

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REFERENCES

1. Chalmers, J.A., Quintana, D.S., Abbott, M.J., et al., 2014. Anxiety disorders are associated with reduced heart rate variability: A meta-analysis. Front. Psychiatry. 5, 80.

2. Quintana, D.S., Westlye, L.T., Kaufmann, T., et al, 2016. Reduced heart rate variability in schizophrenia and bipolar disorder compared to healthy controls. Acta. Psychiatr. Scand. 133, 44-52.

3. Kemp, A.H., Quintana, D.S., 2013 The relationship between mental and physical health: Insights from the study of heart rate variability. Int. J. Psychophysiol. 89, 288ç296.

4. Kemp, A.H., Arias, A.A., Fisher, Z., 2017a. Social ties, health and wellbeing: A literature review and model, in: Ibáñez, A., Sedeño, L., García, A.M. (Eds.), Neuroscience and Social Science: The Missing Link. Springer International, pp. 397-427.

5. Kemp, A.H., Koenig, J., Thayer, J., 2017b. From Psychological Moments to Mortality: A Multidisciplinary Synthesis on Heart Rate Variability Spanning the Continuum of Time. Neurosci. Biobehav. Rev. 83, 547-567.

6. Kemp, A.H., 2018. Toward a transdisciplinary science of health and wellbeing spanning psychological science and epidemiology: a focus on vagal function. Thesis submitted to the University of Melbourne in total fulfilment of the Doctor of Science (DH-SC) degree. Available here: http://hdl.handle.net/11343/222444

7. Alstrom, C.H., 1942. Mortality in mental hospitals. Acta. Psychiatr. Neurol., 17, 1ç42.

8. Tsai, S.Y., Lee, C.H., Chen, P.H., et al., 2017. Risk factors for early cardiovascular mortality in patients with bipolar disorder. Psychiatry. Clin. Neurosci. 71, 716-724.

9. Westman, J., Hällgren, J., Wahlbeck, K., et al., 2013. Cardiovascular mortality in bipolar disorder: A population-based cohort study in Sweden. BMJ Open. 3, e002373

10. Laursen, T.M., Nordentoft, M., 2011. Heart disease treatment and mortality in schizophrenia and bipolar disorder τ changes in the Danish population between 1994 and 2006. J. Psychiatr. Res. 45, 29ς35.

11. Damegunta, S.R., Gundugurti, P.R., 2017. A Cross-sectional Study to Estimate Cardiovascular Risk Factors in Patients with Bipolar Disorder. Indian J. Psychol. Med. 39, 634-640.

12. McIntyre, R.S., Calabrese, J.R., 2019. Bipolar depression: the clinical characteristics and unmet needs of a complex disorder. Curr. Med. Res. Opin. 5, 1-13.

13. Weiner, M., Warren, L., Fiedorowicz, J.G., 2011. Cardiovascular morbidity and mortality in bipolar disorder. Ann. Clin. Psychiatry. 23, 40ς47.

14. Slomka, J.M., Piette, J.D., Post, E.P., et al., 2012. Mood disorder symptoms and elevated cardiovascular disease risk in patients with bipolar disorder. J. Affect. Disord. 138, 405ς408.

15. Task Force of the European Society of Cardiology and North American Society of Pacing Electrocardiography, Heart Rate Variability ς Standards of Measurement, Physiological Interpretation and Clinical Use, 1996. Circulation. 93, 1043-1065.

16. Berntson, G.G., Bigger, J.T., Jr, Eckberg, D.L., et al., 1997. Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology. 34, 623-48.

17. Mather, M., Thayer, J., 2018. How heart rate variability affects emotion regulation brain networks. Curr. Opin. Behav. Sci., 19, 98-104.

18. Porges, S.W., 2009. The polyvagal theory: new insights into adaptive reactions of the autonomic nervous system. Cleve. Clin. J. Med., 76, 86-60.

19. Outhred, T., Kemp, A.H., Malhi, G.S., 2014. Physiological correlates of bipolar spectrum disorders and their treatment, in: Kumari, V., Bob, P., Boutros, N.N. (Eds.). Electrophysiology and Psychophysiology in Psychiatry and Psychopharmacology. Springer International Publishing, pp. 47-102.

20. Wang, X., Cao, P., Xu, L., et al., 2016. Sympathetic skin response and R-R interval variation in the assessment of clinical remission of bipolar disorder. Psychiatry Res. 237, 279-281.

21. Voggt, A., Berger, M., Obermeier, M., et al., 2015. Heart rate variability and Omega-3 Index in euthymic patients with bipolar disorders. Eur. Psychiatry., 30, 228-232.

22. Bassett, D., Bear, N., Nutt, D., et al., 2016. Reduced heart rate variability in remitted bipolar disorder and recurrent depression. Aust. N. Z. J. Psychiatry. 50, 793-804.

23. Wazen, G.L.L., Gregório, M.L., Kemp, A.H., Godoy, M.F., 2018. Heart rate variability in patients with bipolar disorder: From mania to euthymia. J. Psych. Res. 99, 33-38.

24. Kemp, A.H., 2010. Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. Biol. Psychiatry. 67,1067ï1074.

25. Godoy, M.F., 2016. Nonlinear Analysis of Heart Rate Variability: A Comprehensive Review. J. Cardiol. Ther. 3, 528-533.

26. Godoy, M.F, 2019. Gregório ML. Diagnostic Relevance of Recurrence Plots for the Characterization of Health, Disease or Death in Humans. J. Hum. Growth. Dev. 29, 39-47.

27. Wessel, N., Suhrbier, A., Malberg, H., 2009. Detection of time-delayed interactions in biosignals using symbolic coupling Traces. Europhys. Lett. 87, 10004.

28. Angus, D., Smith, A., Wiles, J., 2012. Conceptual recurrence plots: revealing patterns in human discourse. IEEE. Trans. Vis. Comput. Graph. 18, 988-997.

29. Hirata, Y., Aihara, K., 2012. Timing matters in foreign exchange markets. Physica. 391, 760ç 766.

30. Bianchi, F.M., Livi, L., Alippi, C., 2018. Investigating Echo-State Networks Dynamics by Means of Recurrence Analysis. IEEE. Trans. Neural. Netw. Learn. Syst. 29, 427-439.

31. Marwan, N., Donges, J.F., Zou, Y., et al., 2009. Complex network approach for recurrence analysis of time series. Phys. Lett. 373, 4246ç4254.

32. Porta, A., Tobaldini, E., Guzzetti, S., et al., 2007. Assessment of cardiac autonomic modulation during graded head-up tilt by symbolic analysis of heart rate variability. Am. J. Physiol. Heart Circ. Physiol. 293, H702-708.

33. Porta, A., Baumert, M., Cysarz, D., Wessel, N., 2015. Enhancing dynamical signatures of complex systems through symbolic computation. Phil. Trans. R. Soc. A. 373, 2014009.

34. Guzzetti S, Borroni E, Garbelli PE, et al. Symbolic dynamics of heart rate variability: a probe to investigate cardiac autonomic modulation. Circulation. 2005;112(July (4)):465--470.

35. Hoyer, D., Friedrich, H., Zwiener, U., et al., 2006. Prognostic impact of autonomic information flow in multiple organ dysfunction syndrome patients. Int. J. Cardiol. 108, 359-369.

36. Huikuri, H.V., Perkiömäki, J..S, Maestri, R., Pinna, G.D., 2009. Clinical impact of evaluation of cardiovascular control by novel methods of heart rate dynamics. Philos Trans. A. Math. Phys. Eng. Sci. 367, 1223-1238.

37. Amorim, P., 2000. Mini International Neuropsychiatric Interview (MINI): validation of a short structured diagnostic psychiatric interview. Rev. Bras. Psiquiatr. 22, 106-115.

38. Shansis, F., Berlim, M.T., Mattevi, B., et al., 2004. Desenvolvimento da versão em português da Escala de Avaliação de Mania de Bech-Rafaelsen (EAM-BR). ver. Psiquiatr. RS. 26, 30-38.

39. Quintana DS, Alvares GA, Heathers JA. Guidelines for Reporting Articles on Psychiatry and Heart rate variability (GRAPH): recommendations to advance research communication. Transl Psychiatry. 2016;6(5):e803.

40. Anderson PO, Knoben JE, Troutman WG. Lithium. In: Anderson PO, Knoben JE, Troutman WG. Handbook of Clinical Drug Data. 10. ed., Nova York: Mc Graw-Hill, 2002. 480 p.

41. Catai, A.M., Pastre, C.M., Godoy, M.F., et al., 2019. Heart rate variability: are you using it properly? Standardization checklist of procedures. Braz. J. Phys. Ther. pii: S1413-3555(18)30797-30794.

42. Vanderlei, L.C., Silva, R.A., Pastre, C.M., et al., 2008. Comparison of the Polar S810i monitor and the ECG for the analysis of heart rate variability in the team and frequency domains. Braz. J. Med. Biol. Res. 41, 854-859.

43. Voss, A., Baier, V., Schulz, S., Bar, K.J., 2006. Linear and nonlinear methods for analyses of cardiovascular variability in bipolar disorders. Bipolar Disord. 8, 441-452.

44. Porta, A., Guzzetti, S., Montano, N., et al., 2001. Entropy, entropy rate, and pattern classification as tools to typify complexity in short heart period variability series. IEEE Trans. Biomed. Eng. 48, 1282-1291.

45. Santos, L., Barroso, J.J., Macau, E.E., de Godoy, M.F., 2013. Application of an autonomic adaptative filter for Heart Rate Variability analysis. Med. Eng. Phys. 35, 11778-11785.

46. Cohen, J., 1998. Statistical power analysis for the behavioral sciences, second ed. Hillsdale, NJ: Lawrence Earlbaum Associates.

47. Carr, O., de Vos, M., Saunders, K. E., 2018. Heart rate variability in bipolar disorder and borderline personality disorder: a clinical review. Evid. Based Ment. Health. 21, 23-30.

48. de la Torre-Luque, A., Bornas, X., Balle, M., Fiol-Veny, A., 2016. Complexity and nonlinear biomarkers in emotional disorders: A meta-analytic study. Neurosci. Biobehav. Rev. 68, 410-422.

49. Faurholt-Jepsen, M., Kessing, L. V., Munkholm, K., 2017. Heart rate variability in bipolar disorder: a systematic review and meta-analysis. Neurosci. Biobehav. Rev. 73, 68-80.

50. Krane-Gartiser, K., Henriksen, T.E., Morken, G., Vaaler, A., Fasmer, O.B., 2014. Actigraphic assessment of motor activity in acutely admitted inpatients with bipolar disorder. PLoS One. 9, e89574.

51. Migliorini, M., Mendez, M. O., Bianchi, A. M., 2012. Study of heart rate variability in bipolar disorder: linear and non-linear parameters during sleep. Front. Neuroeng. 4, 22.

52. Henry, B. L., Minassian, A., Paulus, M. P., Geyer, M. A., Perry, W., 2010. Heart rate variability in bipolar mania and schizophrenia. J. Psychiatr. Res. 44, 168-176.

53. Hu, M.X., Lamers, F., de Geus, E.J., Penninx, B.W., 2016. Differential Autonomic Nervous System Reactivity in Depression and Anxiety During Stress Depending on Type of Stressor. Psychosom. Med. 78, 562-572.

54. van Os, J., 2013. The dynamics of subthreshold psychopathology: implications for diagnosis and treatment. Am. J. Psychiatry. 170, 695-698.

55. Valenza, G., Nardelli, M., Lanata', A., et al., 2016. Predicting Mood Changes in Bipolar Disorder through Heartbeat Nonlinear Dynamics. IEEE J Biomed Health Inform. 20, 1034-1043.

56. Khatana, S.A., Kane, J., Taveira, T.H., et al., 2011. Monitoring and prevalence rates of metabolic syndrome in military veterans with serious mental illness. PLoS One. 6, e19298.

57. Chesney, E., Goodwin, G.M., Fazel, S., 2014. Risks of all-cause and suicide mortality in mental disorders: a meta-review. World Psychiatry. 13, 153-160.

58. Dome, P., Rihmer, Z., Gonda, X., 2019. Suicide Risk in Bipolar Disorder: A Brief Review. Medicina (Kaunas). 55, pii: E403.

59. Martinez-Aran, A., Bonnin, C.M., Torrent, C., Solé, B., Torres, I., Jiménez, E., 2017. Cognição e Progressão da Doença no Transtorno Bipolar. In: Kapczinski, F., Vieta, E., Magalhães, P.V.S., Berk, M. (Eds.), Neuroprogressão e Estadiamento no Transtorno Bipolar. Artmed, Porto Alegre.

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61. Strejilevich, S., Martino, D.J., 2017. Cognição Social e Estadiamento do Transtorno Bipolar. In: Kapczinski, F., Vieta, E., Magalhães, P.V.S., Berk, M. (Eds.), Neuroprogressão e Estadiamento no Transtorno Bipolar. Artmed, Porto Alegre.

62. Todder, D., Bersudsky, Y., Cohen, H., 2005. Nonlinear analysis of RR interval in euthymic bipolar disorder. Auton. Neurosci. 117, 127ς31.

Figure legends

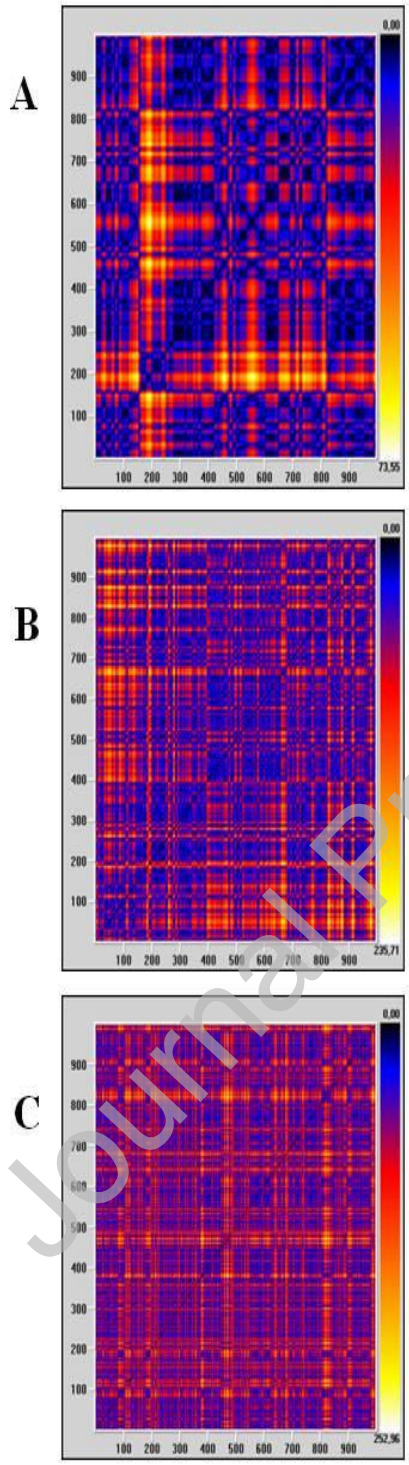

Figure 1. A representative case of Recurrence Plot visual patterns of each group: A) Pre-treatment - manic state; B) Post-Treatment ς euthymic state; and C) Controls - without BD.

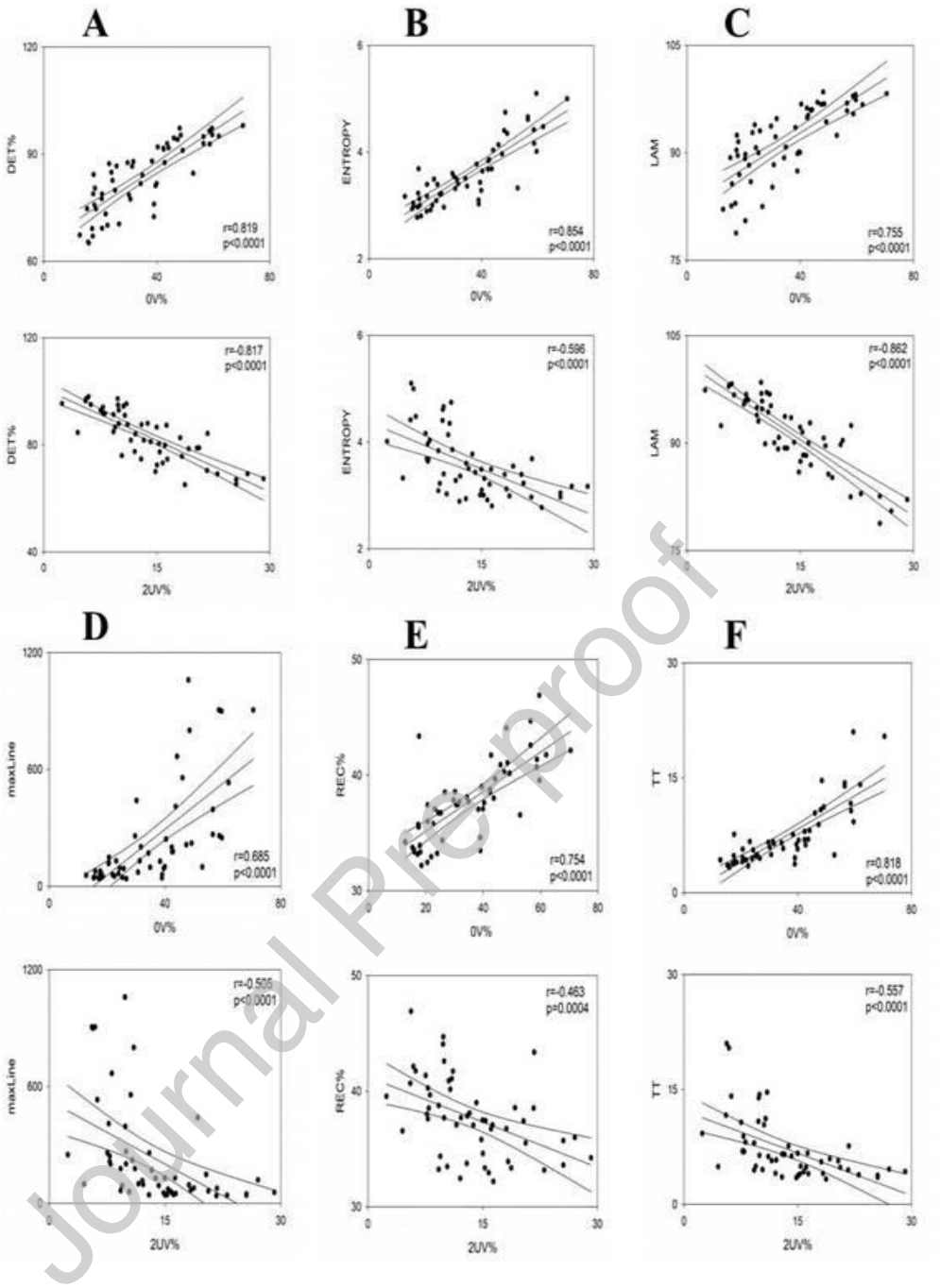

Figure 2. Correlation between HRV indices in RP and SA methods for all studied groups. A, 0V% or 2UV% pattern of symbolic analysis with DET%; B, 0V% or 2UV% pattern with Shannon Entropy; C, 0V% or 2UV% pattern of symbolic analysis with LAM; D, 0V% or 2UV% pattern of symbolic analysis with maxLine; E, 0V% or 2UV% pattern of symbolic analysis with REC%; F, 0V% or 2UV% pattern of symbolic analysis with TT.

Table 1. Age, symbolic and complexity analysis, and recurrence variables indices of HRV.

Variables	Controls	Mania	Euthymia	Group difference (p-value)		
	(a)	(b)	(c)	a x b	b x c	a x c
Age	33.9±10.8	33.1±12.0	33.1±12.0	0.9711	0.9711	>0.9999
Symbolic Analysis						
0V%	28.37±12.9	46.68±14.09	29.97±11.74	0.0003*	0.0009*	0.9273
1V%	47.67±5.07	40.51±8.28	47.38±4.99	0.0036*	0.0054*	0.9898
2LV%	7.60±4.71	3.67±4.16	7.54±4.69	0.0322*	0.0356*	0.0584
2UV%	16.39±6.43	9.18±3.32	15.02±5.69	0.0005*	0.005*	0.7235
Complexity analysis						
Shannon Entropy	3.32±0.37	3.13±0.39	3.50±0.35	0.2758	0.0124*	0.3399
Recurrence analysis						
REC%	37.1±4.1	39.4±3.7	36.6±2.7	0.1324	0.0488*	0.8885
DET%	76.5±11.1	90.5±6.7	81.9±8.1	<0.0001*	0.0129*	0.1678
LAM	87.2±6.7	95.0±3.0	90.7±4.1	<0.0001*	0.0266*	0.0928
TT	5.0±1.9	10.2±5.0	6.1±2.5	0.0001*	0.0023*	0.6045
ShanEntr	3.2±0.5	4.0±0.7	3.4±0.4	0.0003*	0.0067*	0.5637
Lmax	86.9±63.1	383.7±304.6	113.00±66.7	<0.0001*	0.0002*	0.9048

Data are expressed as mean ± standard deviation; One Way ANOVA with Tukey Post-test.

Table 2. Effect size evaluation (*d* Cohen) and correlation values (r) after treatment in bipolar disorder.

Variables	Mania	Euthymia	d	R
REC%	39.4±3.7	36.6±2.7	0.8888	0.4061
DET%	90.5±6.7	81.9±8.1	1.1595	0.5016
LAM	95.0±3.0	90.7±4.1	1.2041	0.5158
TT	10.2±5.0	6.1±2.5	1.0126	0.4517
ShanEntr	4.0±0.7	3.4±0.4	1.0341	0.4593
Lmax	383.7±304.6	113.00±66.7	1.2276	0.5231

Data are expressed as mean ± standard deviation and absolute Y ŜI·ădzWŜă 2Ŧ / 2ĸSyDă *d* effect size and its correlation values (r).

Table 3. Linear analysis (time and frequency domain) in the manic phase and in the euthymic phase, compared to the control group.

Variables	Controls	Mania	Euthymia	P- value		
	(a)	(b)	(c)	a x b	b x c	a x c
Time domain Analysis						
Mean RR	919.6±103.4	712.8±87.7	796.6±102.5	<0.0001*	0.0353*	0.0012*
STD (ms)	43.3(26.5-53.7)	21.8(9.7-28.6)	20.4(12.5-35.2)	<0.05*	-	<0.05*
SDNN	47.1±15.5	35.5±18.5	38.7±22.2	0.1681	0.8701	0.3836
Frequency domain analysis						
LF abs	746.8(332.5-1064.8)	347.7(53.6-529.7)	238.4(63.7-614.4)	<0.05*	-	<0.05*
LF nu	73.7±16.4	81.3±9.6	67.3±14.4	0.237	0.011*	0.354
HF abs	153.0(111.9-313.1)	71.4(10.8-94.8)	110.5(19.1-380.8)	<0.05*	-	-
HF nu	26.2±16.4	18.6±9.6	32.5±14.4	0.232	0.011*	0.363

Data are expressed as mean ± standard deviation; One Way ANOVA with Tukey Post-test.

Table 4. Correlation between heart rate variability RP and SA indices.

	REC%	DET%	LAM	TT	Entropy	maxLine
All volunteers						
%0V	0.753*	0.819*	0.755*	0.818*	0.854*	0.685*
%1V	-0.747*	-0.669*	-0.576*	-0.839*	-0.831*	-0.658*
%2LV	-0.708*	-0.585*	-0.461*	-0.646*	-0.732*	-0.553*
%2UV	-0.463*	-0.817*	-0.862*	-0.557*	-0.596*	-0.505*
Control Group						
%0V	0.515#	0.729#	0.632#	0.594#	0.687#	0.609#
%1V	-0.628#	-0.585#	-0.397	-0.607#	-0.607#	-0.543#
%2LV	-0.411	-0.385	-0.196	-0.432	-0.529#	-0.464
%2UV	-0.243	-0.722#	-0.813*	-0.401	-0.514#	-0.456
Mania Group						
%0V	0.804	0.778	0.768#	0.825	0.856	0.689#
%1V	-0.812	-0.746#	-0.705#	-0.848	-0.861	-0.676#
%2LV	-0.774#	-0.638#	-0.627#	-0.685#	-0.775#	-0.580#
%2UV	-0.413	-0.643#	-0.716#	-0.496#	-0.404	-0.479#
Euthymia Group						

%0V	0.871*	0.801*	0.734*	0.869*	0.859*	0.837*
%1V	-0.613#	-0.461	-0.416	-0.794*	-0.758#	-0.614#
%2LV	-0.886*	-0.529#	-0.383	-0.690#	-0.774#	-0.693#
%2UV	-0.551#	-0.848*	-0.869*	-0.543#	-0.489#	-0.635#

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