

Point-process Nonlinear Autonomic Assessment of Depressive States in Bipolar Patients

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Keywords

Bipolar Disorder, Heart Rate Variability (HRV), Point Process, High Order Statistics, Bispectrum, Nonlinear Analysis, Wiener-Volterra Series, International Affective Picture System (IAPS), Thematic Apperception Test (TAT)

Summary

Introduction: This article is part of the Focus Theme of *Methods of Information in Medicine* on “Biosignal Interpretation: Advanced Methods for Studying Cardiovascular and Respiratory Systems”.

Objectives: The goal of this work is to apply a computational methodology able to characterize mood states in bipolar patients through instantaneous analysis of heartbeat dynamics.

Methods: A Point-Process-based Nonlinear Autoregressive Integrative (NARI) model is applied to analyze data collected from five bipolar patients (two males and three females, age 42.4 ± 10.5 range 32–56) undergoing a dedicated affective elicitation protocol using images from the International Affective Picture System (IAPS) and Thematic

Apperception Test (TAT). The study was designed within the European project PSYCHE (Personalised monitoring SYstems for Care in mental HEalth).

Results: Results demonstrate that the inclusion of instantaneous higher order spectral (HOS) features estimated from the NARI nonlinear assessment significantly improves the accuracy in successfully recognizing specific mood states such as euthymia and depression with respect to results using only linear indices. In particular, a specificity of 74.44% using the instantaneous linear features set, and 99.56% using also the nonlinear feature set were achieved. Moreover, IAPS emotional elicitation resulted in a more discriminant procedure with respect to the TAT elicitation protocol.

Conclusions: A significant pattern of instantaneous heartbeat features was found in depressive and euthymic states despite the inter-subject variability. The presented point-process Heart Rate Variability (HRV) nonlinear methodology provides a promising application in the field of mood assessment in bipolar patients.

1. Introduction

Bipolar disorder is a cyclic psychiatric condition in which patients experiencing episodes of either pathological depression or manic or hypomanic episodes. These subjects can also experience episodes in which depressive and manic symptoms are present at the same time (mixed episodes). Mood states with relatively good affective balance are defined as “euthymia”. Despite the prevalence and high cost of mood disorders [1], this illness may go undetected for years before it is diagnosed and treated. Currently, the patient’s mood is assessed by clinician-administered rating scales and no biological markers nor physiological signals highlighted in research studies are used for clinical purposes [2].

The overarching goal of this research study is to be able to accurately discern depressive and euthymic states in bipolar patients (BPs) from the analysis of non-invasive physiological signals. Data were gathered within the European project PSYCHE (Personalised monitoring SYstems for Care in mental HEalth) [3], which was funded in the Seventh Framework Programme. The PSYCHE system comprises a personal, pervasive, cost-effective, and multi-parametric monitoring system based on textile platforms and portable sensing devices for the long term (i.e., up to 24 hours of recordings during an unstructured activity) and short term (i.e., up to 30 minutes of recordings during a structured activity) acquisition of data from a selected class of patients affected by mood disorders, i.e., BPs. In this study, the core

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sensing system of the project, hereinafter referred to as the PSYCHE platform, was taken into account while considering short term acquisitions. The platform consists of a comfortable, textile-based sensorized t-shirt, including fabric-based electrodes. Several physiological signals such as ECG, movement and respiration activities, as well as behavioral parameters such as quantifiers of activity using a smartphone and mood agenda through the Bauer internal mood scale [4] can be gathered through the PSYCHE platform [3]. Our analysis focuses on the heartbeat intervals (RR series) extracted from the ECG, i.e. the series constituted by the time intervals of two consecutive peaks of the ECG. Hypothesizing that the autonomic nervous system (ANS) exerts different time-varying RR dynamics according to the patient's mood state, in fact, computational tools able to discern rapid dynamic changes with high time resolution could provide an optimal assessments [3, 5]. To this extent, a point-process nonlinear derivative model has been applied to estimate the instantaneous auto-spectrum and bispectrum in short term recordings and under nonstationary conditions [6–8, 25]. This powerful, fully-parametric statistical tool accounts for the probabilistic generative mechanism of the heartbeat, further considering a quadratic Wiener-Volterra representation of the first order moment of a physiological plausible inverse-Gaussian statistics [9]. Spectral and bispectral instantaneous RR measures can then be derived from the linear and nonlinear coefficients, respectively. As the framework is defined in continuous time, it is possible to estimate instantaneous heart

rate (HR) and heart rate variability (HRV) indices without using any interpolation method. Experimental results, shown in section 3, report on different emotional elicitation protocols as well as demonstrate how the inclusion of higher order spectral (HOS) features can improve the specificity of our system by 25.12% while reducing its uncertainty (variance) by 17.82% considering ANS euthymic and depressive patterns.

2. Methods

In order to obtain linear and nonlinear estimates of ANS dynamics, we propose to apply a Nonlinear Autoregressive Integrative (NARI) Model linked to an equivalent second-order input-output Volterra model [10, 11] (►Figure 1), where $y(k)$ is the discrete time series (in our case the RR interval series), $\{y_0, y_1, y_2\}$ are the autoregressive coefficients of the Wiener-Volterra terms, M is the memory of the autoregressive terms, and $\varepsilon(k)$ are independent, identically distributed Gaussian random variables. The NARI representation models the differenced time series in order to improve on the stationary requirements of the time series by the elimination of drift. Therefore, the model output needs to be integrated to forecast the original series. A quadratic order of the autoregressive series in Eq. 1 (►Figure 1)(i.e., $n = 2$) retains an important part of the non-linearity of the system and allows the evaluation of the high order statistics (HOS), such as the dynamic bispectrum [12]. Let $(0, T]$ denote the observation interval, the ordered set of times of the R-wave events recorded in $(0, T]$, $RR_j =$

$u_j - u_{j-1} > 0$, the j^{th} R-R interval. Then, assuming history dependence, we embed the NARI representation within the probability distribution of the waiting time $t - u_j$ until the next R-wave event, which follows an inverse-Gaussian model [9]. Thus, the variable $\mu_{RR}(t, \mathcal{H}_t, \xi(t))$ represents the first-moment statistic (mean) of the distribution (►Figure 2).

The coefficients $y_0, \{y_1(i)\}, \{y_2(i, j)\}$ correspond to the time-varying zero-, first-, second-order NARI coefficients, respectively. Considering the derivative R-R series improves the achievement of stationarity within the sliding time window W (in this work we have chosen $W = 90$ seconds by preliminary KS plots goodness-of-fit analysis [9, 13]). Given the proposed parametric model, the instantaneous nonlinear HRV indices will be updated as a time-varying function of the parameters $\xi(t) = [\theta(t), y_0(t), y_1(1, t), \dots, y_1(p, t), y_2(1, 1, t), \dots, y_2(i, j, t)]$ with an arbitrarily small bin size (milliseconds). A local maximum likelihood method [9] is used to estimate the unknown time-varying parameter set $\xi(t)$. We can determine the optimal order based on the Akaike Information Criterion $AIC = -2L + 2\dim(\xi)$, where L is the maximized value of the likelihood function for the estimated model. Once the order $\{p, q\}$ is determined, the initial NARI coefficients are estimated by least squares. The goodness-of-fit of the point process model is based on the Kolmogorov-Smirnov (KS) test [9], derived from the time-rescaling theorem [9], between the transformed R-R intervals [9] and uniform probability density on interval $(0,1]$. The smaller the KS distance, the closer the agreement between the model and the original R-R interval series. Transformed quantiles' autocorrelation plots are also considered to test independence of the model-transformed intervals [9]. The input-output model of a nonlinear dynamic system can be written using Wiener-Volterra series [6, 7] and its representation is needed to estimate the dynamical spectra and bispectra of the series.

In particular, the quadratic NARI models can be linked to the traditional input-output Volterra models by using the relationships [14] between the Fourier transforms of the Volterra kernels of order k ,

$$y(k) = \gamma_0 + \sum_{i=1}^M \gamma_1(i) y(k-i) + \sum_{n=2}^{\infty} \sum_{i_1=1}^M \dots \sum_{i_n=1}^M \gamma_n(i_1, \dots, i_n) \prod_{j=1}^n y(k-i_j) + \varepsilon(k)$$

Figure 1 Equation 1

$$\begin{aligned} \mu_{RR}(t, \mathcal{H}_t, \xi(t)) = & RR_{\tilde{N}(t)} + \gamma_0 + \sum_{i=1}^p \gamma_1(i, t) (RR_{\tilde{N}(t)-i} - RR_{\tilde{N}(t)-i-1}) \\ & + \sum_{i=1}^q \sum_{j=1}^q \gamma_2(i, j, t) (RR_{\tilde{N}(t)-j} - RR_{\tilde{N}(t)-j-1}) \end{aligned}$$

Figure 2

$H_k(f_1, \dots, f_n)$, and the Fourier transforms of the NARI kernels, $\Gamma_1'(f_1)$ and $\Gamma_2'(f_1, f_2)$.

Given the input-output Volterra kernels of the NARI model for the instantaneous R-R interval mean $\mu_{RR}(t, \mathcal{H}_t, \xi(t))$, the time-varying parametric (linear) autospectrum of the derivative series is [6, 7]:

$$Q(f, t) = S_{xx}(f, t) H_1(f, t) H_1(-f, t) \quad (2)$$

where $S_{xx}(f, t) = \sigma_{RR}^2$. The time-varying parametric autospectrum of the R-R intervals is given by multiplying its derivative spectrum $Q(f, t)$ by the quantity $2(1 - \cos(\omega))$ [13]. By integrating ▶Equation 2 in each frequency band, we compute the index within the LF (0.04–0.15 Hz) and HF (0.15–0.5 Hz) ranges [15]. The ratio between the LF component and the HF component has been pointed out as an index of sympatho-vagal balance [15]. The bispectrum of a nonlinear system response subject to stationary, zero-mean Gaussian input [16] can be computed from the Fourier transform of the second-order Volterra kernel coefficients $H_2(f_1, f_2, t)$ [6, 7].

We evaluated three bispectral measures by integrating in the appropriate frequency bands [6, 7]:

$$LL(t) = \int_{f_1=0^+}^{0.15} \int_{f_2=0^+}^{0.15} \text{Bis}(f_1, f_2, t) df_1 df_2; \quad (3)$$

$$LH(t) = \int_{f_1=0^+}^{0.15} \int_{f_2=0.15^+}^{0.4} \text{Bis}(f_1, f_2, t) df_1 df_2; \quad (4)$$

$$HH(t) = \int_{f_1=0.15^+}^{0.4} \int_{f_2=0.15^+}^{0.4} \text{Bis}(f_1, f_2, t) df_1 df_2 \quad (5)$$

▶Equations 3 and 4 can be interpreted as an index of nonlinear interaction between the sympathetic and the parasympathetic

system, whereas ▶Equation 5 can be exclusively attributed to nonlinear vagal dynamics. In fact, by extending to the bispectra important concepts demonstrated for standard HRV spectral analysis [17], it seems reasonable to hypothesize that the double integration performed on the LF bands on the bispectral plane (i.e., the LL index) as well as the integration performed on the LF and HF bands on the bispectral plane (i.e., the LH index), provides biomarkers which are affected by both sympathetic and parasympathetic nervous system activity, whereas the double integration performed on the HF bands on the bispectral plane (i.e., the HH index) provides a biomarker affected by parasympathetic tone exclusively.

3. Experimental Protocol and Results

We applied our point process-based method to data gathered from five bipolar patients undergoing a dedicated affective elicitation protocol. The patients were recruited according to the PSYCHE project exclusion/inclusion criteria:

- Age 18–65;
- Diagnosis of bipolar disorder with an active episode at the moment of recruitment;
- Absence of delusions and/or hallucinations;
- Absence of substance abuse disorder;
- Absence of relevant somatic or neurological conditions.
- Absence of suicidal risk;
- Possibility to provide a written informed consent.

More in detail, BP1 (37 years old, female) was acquired during the euthymic phase, BP2 (36 years old, male) during the depressive phase, BP3 (32 years old, female) underwent two sessions during the depressive (first) and euthymic (second) phases, BP4 (56 years old, female) underwent two recording sessions, both during a depressive state, whereas BP5 (52 years old, male) underwent five recording sessions, four of which during a depressive state and one during the euthymic (fifth) phase. All the patients were in treatment with mood stabilizers and antipsychotic medications. BP1, BP2, BP3 and BP4 were also under Selective serotonin re-uptake inhibitors (SSRI) antidepressant treatment. Of note, BP4 and BP5 underwent also electroconvulsive treatment (ECT). It is worthwhile noting that the additional ECT treatment does not affect the possibility to include these patients into our analyses. As a matter of fact, the whole PSYCHE system has been developed to study the ANS dynamics in patients with bipolar disorders despite their clinical heterogeneity and the differences in treatment. Therefore, although we are not able to evaluate specific patterns of ANS changes related to a given type of treatment (or of clinical phenotype), we are able to evaluate the common ANS dynamical signatures underpinning the psychophysiological changes in bipolar disorder.

The proposed experimental paradigm took place in a visiting room of the Santa Chiara University Hospital, Pisa (Italy). The room was illuminated with artificial neon-light. In order to avoid surrounding noise, the acquisitions were taken during the afternoon while the normal routine ac-

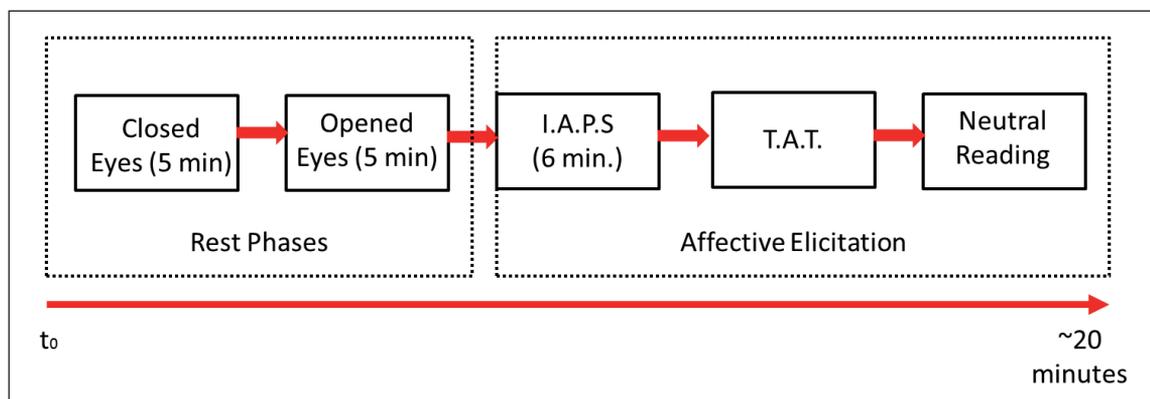
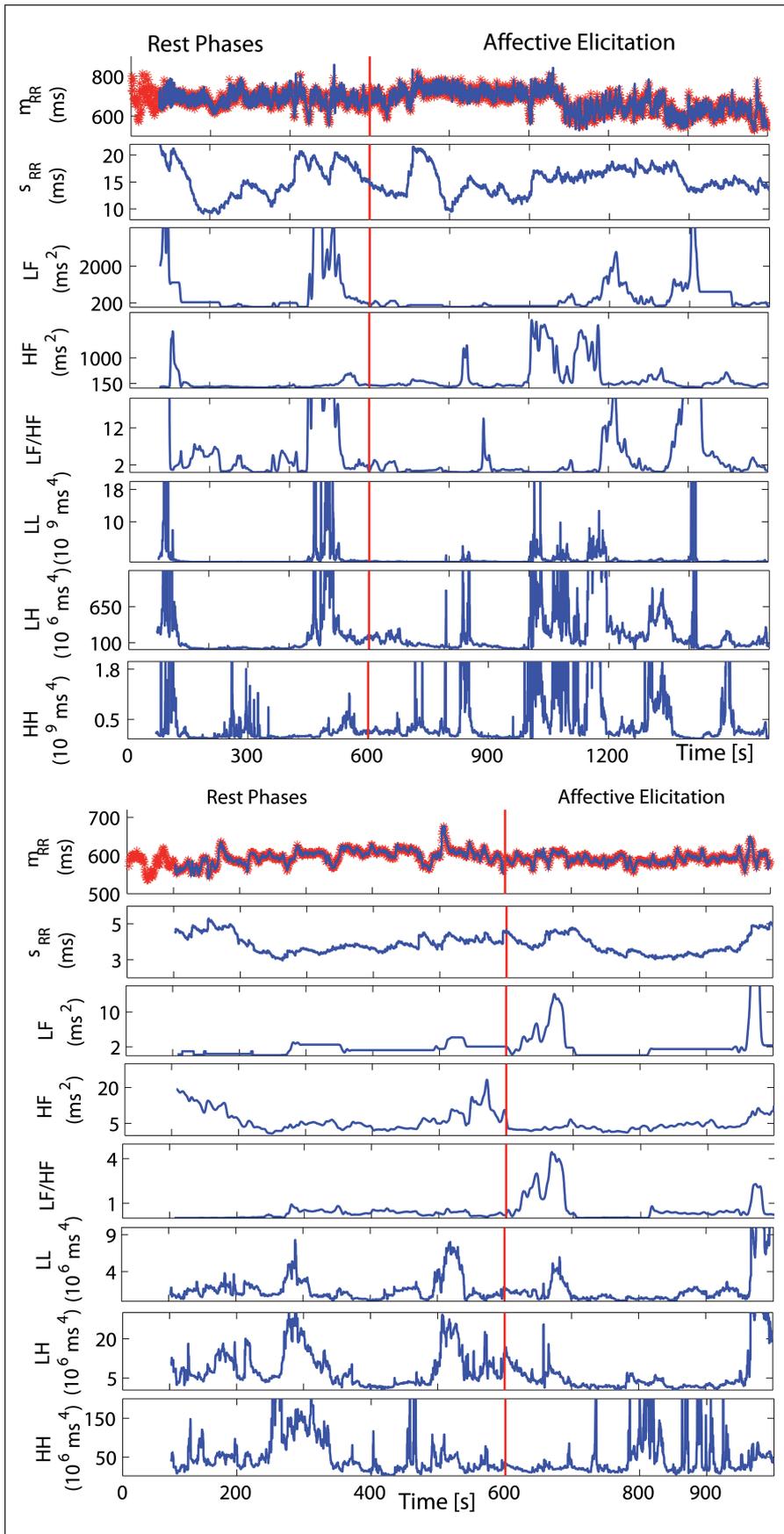


Figure 3 Block scheme of the experimental protocol for emotion elicitation in bipolar patients



tivity in the other rooms were over. At hospital admission a “mood label” (i.e. “euthymia” or “depression”) was assigned and used as a class label for further evaluations. ECG signals were acquired, with sample frequency of 250 Hz, by having the subject wear a sensorized shirt. Patients were asked to sit in a comfortable position. Each visit/recording session of the dedicated affective elicitation protocol started with two five minutes lasting phases of resting state, with eyes closed and open respectively. Subsequently, a passive (IAPS), and an active (TAT) visual stimuli were administered. IAPS stands for International Affective Picture System [18]. The IAPS protocol implies a slideshow of pictures, presented on a laptop screen (17 inch) at a distance of about 20 cm, having two classes of arousal, either minimum or maximum, and random valence, ranging from unpleasant to pleasant. IAPS were presented in blocks of two minutes each of high arousal negative pictures alternated with two minutes high arousal neutral pictures. Two cycles of negative and neutral pictures were presented. After the IAPS elicitation, patients were asked to describe several TAT images. TAT stands for Thematic Apperception Test, a projective psychological test. The TAT is supposed to tap a subject’s unconscious to reveal repressed aspects of personality, motives and needs for achievement, power and intimacy, and problem-solving abilities. However, in this protocol the pictures were only used to elicit spontaneous comments from the patients. Of note, as there is no standardization of the use of the texts/pictures according to the subjects clinical state, text/picture stimuli were always proposed in the same order. A schematic timeline of the experimental protocol is shown in ► Figure 3. The NARI model was applied to RR series detected

Figure 4 Instantaneous HRV statistics computed from BP1 (top) and BP2 (bottom) during the euthymic and depressive state, respectively. The estimated $\mu_{RR}(t, \mathcal{H}_t, \xi(t))$ is superimposed on the recorded RR series. Following below, the instantaneous heartbeat standard deviation, the instantaneous heartbeat spectral Low frequency (LF) and High frequency (HF) powers and their ratio. Finally, bottom rows report the three Bispectral statistics (Eqs. 5, 6, and 7).

from the recorded ECG. The optimal model was chosen by means of the Akaike Information Criterion (AIC) [9] applied to the first 5-min RR recordings. The AIC analysis indicated $6 \leq p \leq 8$ and $1 \leq q \leq 2$ as optimal orders. The obtained KS distances were no greater than 0.04. Seven out of the eleven KS plots were inside the 95% confidence intervals and four had only 4% points outside. No less than 97% of the autocorrelation points were inside the boundaries. The linear and nonlinear indices were evaluated for all of the patient's acquisition. The instantaneous identification (5 ms resolution) was averaged within a time window of 1 second. About 1200 multiple feature points along the time were obtained for each visit/acquisition. Representative tracking results are shown in ►Figure 4 for Subject 1 (Euthymic phase, top) and Subject 2 (Depressed phase, bottom). Of note, the depressed phase is associated to a reduced RR variability as well as spectral and bispectral power. An inter-subject analysis was performed to reveal the common mood pattern among patients. Discrimination of the mood states was performed using the well-known Multilayer Perceptron (MLP) Neural Network [19]. In this work, the MLP implementation included three layers of neurons: input, hidden, and output layers. The input layer was formed by 8 neurons, one for each of the feature space dimension. The hidden layer was constituted by an empirically estimated number of neurons. Specifically, we chose this number as the upper limit of the half difference between the number of the input and output neurons, i.e. 3. The output layer was formed by 2 neurons, one for each of the considered classes to be recognized. All the results are expressed in the form of confusion matrix, after 40-fold cross validation [20]. The feature dataset was a matrix with a number of rows of about 11×1200 , i.e. number of acquisitions \times number of repeated measures for each acquisition, and up to 8 columns (see details below on the α and β sets). The training phase was carried out on 80% of the feature dataset while the testing phase was on the remaining 20% with the constraint that each acquisition can be either considered as belonging to the training or test set. In particular, for each of the 40

Table 1 Results for the inter-subject Euthymia-Depression Discrimination in patients BP1, BP2, and BP3 using linear and nonlinear features gathered from the point process NARI model during the emotional elicitation protocol, i.e., IAPS and TAT.

MLP-3 Patients	Dataset IAPS-TAT	Euthymia	Depression
Euthymia	α	93.26 \pm 2.98	5.88 \pm 1.99
	β	99.33 \pm 0.46	2.41 \pm 0.94
Depression	α	6.74 \pm 2.98	94.12 \pm 1.99
	β	0.67 \pm 0.46	97.59 \pm 0.94

Bold indicates the best classification accuracy for each mood class.

Table 2 Results for the inter-subject Euthymia-Depression Discrimination in patients BP1, BP2, BP3, BP4, and BP5 using linear and nonlinear features gathered from the point process NARI model during the emotional elicitation protocol, i.e., IAPS and TAT.

MLP-5 Patients	Dataset IAPS-TAT	Euthymia	Depression
Euthymia	α	74.44 \pm 18.21	1.09 \pm 1.92
	β	99.56 \pm 0.39	0.02 \pm 0.06
Depression	α	25.56 \pm 18.21	98.91 \pm 1.92
	β	0.44 \pm 0.39	99.98 \pm 0.06

Bold indicates the best classification accuracy for each mood class.

validation steps, the examples associated to the training and testing set are randomly chosen among all the available examples and results are described as mean and standard deviation among the 40 confusion matrices obtained. This procedure allows to obtain unbiased results on the recognition accuracy. We compared the MLP accuracy by creating two feature sets. The first set, α , is composed by all the linearly-derived features such as $\mu_{RR}(t, \mathcal{H}, \xi(t))$, σ_{RR} , and the spectral indices LF, HF, and LF/HF. The second set, β , concatenates the nonlinear LL, LH, and HH indices to ones defined within the α set.

Experimental results are shown in ►Tables 1–4, always comparing the use of linear and nonlinear features gathered from the point process NARI model. Concerning the two emotional elicitation protocols, i.e., IAPS and TAT, ►Table 1 shows the results for the inter-subject euthymia-depression discrimination using data from patients BP1, BP2, and BP3, i.e., the three patients having the same treatment which did not involve electroconvulsive therapy, whereas ►Table 2 shows the results considering the five BPs. These results indicate the importance of the inclu-

sion of nonlinear dynamics in assessing BPs' reactions to affective stimuli. The use of LL, LH, and HH, in fact, not only improved on the linearly-derived classification accuracy, but also provided consistent and very satisfactory classification accuracy when considering patients who underwent the electroconvulsive therapy. Accordingly, the specificity calculated using the α set on BP1, BP2, and BP3 significantly decreased from 93.26% to 74.44%, while the specificity calculated using the β remained unaltered (about 99%). Concerning all of the misclassified samples, a plausible interpretation can be related to either algorithmic/mathematical artifacts or physiological outliers, i.e. events not related to mood markers for whatever reason. In order to investigate the contribution of the IAPS and TAT emotional elicitation, we performed two further classifications considering feature points exclusively related to either a IAPS or TAT session. Results shown in ►Table 3 and ►Table 4 indicate that the use of IAPS elicitation allows to better discriminate depressive from euthymic states than the use of TAT images. In fact, the specificity using feature points related to the TAT emotional elicitation was only 84.4% using the β set.

Table 3 Results for the inter-subject Euthymia-Depression Discrimination in patients BP1, BP2, BP3, BP4, and BP5 using linear and nonlinear features gathered from the point process NARI model during the IAPS emotional elicitation protocol.

MLP-5 Patients	Dataset IAPS	Euthymia	Depression
Euthymia	α	86.33 \pm 2.60	0.86 \pm 0.73
	β	98.17 \pm 2.59	1.89 \pm 2.67
Depression	α	13.67 \pm 2.60	99.14 \pm 0.73
	β	1.83 \pm 2.59	98.11 \pm 2.67

Bold indicates the best classification accuracy for each mood class.

Table 4 Results for the inter-subject Euthymia-Depression Discrimination in patients BP1, BP2, BP3, BP4, and BP5 using linear and nonlinear features gathered from the point process NARI model during the TAT emotional elicitation protocol.

MLP-5 Patients	Dataset TAT	Euthymia	Depression
Euthymia	α	70.64 \pm 15.57	0.52 \pm 0.73
	β	84.40 \pm 1.30	0.34 \pm 0.49
Depression	α	29.36 \pm 15.57	99.48 \pm 0.73
	β	15.60 \pm 1.30	99.66 \pm 0.49

Bold indicates the best classification accuracy for each mood class.

This finding is in agreement with the current literature reporting that a IAPS session is able to elicit a more discerning-capable significant sympathetic activity (evaluated through the electrodermal activity) in bipolar patients than TAT elicitation [21, 24].

4. Discussion and Conclusion

Along the conceptual framework behind the PSYCHE project, we here present an application for the assessment of ANS patterns of depression in bipolar patients. Data from five participants undergoing a dedicated affective elicitation protocol were acquired during the depressive and euthymic phase. A comfortable, textile-based sensorized t-shirt was used to perform noninvasive recordings of physiological variables, and a point-process NARI model was implemented and applied to the RR series derived from the ECG in order to produce instantaneous features of HRV. In particular, standard features from both the time (i.e. $\mu_{RR}(t, \mathcal{H}_t, \xi(t))$ and σ_{RR}), and frequency domain (i.e. LF, HF, and LF/HF) along with HOS nonlinear features, i.e. LL,

LH, and HH, were extracted from the processed RR series. The NARI model allows for the instantaneous estimation of all these HRV measures without any interpolation method and providing also goodness-of-fit measures. Pattern recognition algorithms (MLP) were then applied to the estimated features to classify the mood state of the patients (i.e. “euthymia” or “depression”), and two feature sets were compared. The first set, α , was composed by only the standard HRV feature set, whereas the nonlinear indices were added to the α set to create the second set, β . In conclusion, a discerning pattern of instantaneous heart-beat features (i.e., statistically significant differences of linear and nonlinear features derived from the NARI modeling of the RR intervals) was found despite the inter-subject variability. Our results show that the inclusion of the nonlinear indices, β set, gives higher accuracy and smaller variance with respect to the classification performed by using only the α set (i.e. the standard linear features). Moreover, these results suggest that a IAPS emotional elicitation can be more effective in discriminating different mood states of the bipolar disorder. One could speculate that the higher dis-

crimination might be due to higher IAPS arousal effects in key central autonomic network areas such as the prefrontal cortex and amygdala. Given their preliminary nature, these results are very promising. The point-process HRV nonlinear analysis, in fact, represents a new approach in the field of mood assessment in bipolar patients. We are aware that this preliminary study does not provide clinical diagnostic value. However, our aim is to propose a methodology based on the point-process HRV nonlinear analysis which allows for consideration of the underlying information of the autonomic nervous systems time-varying dynamics. We have also demonstrated that our methods are able to characterize instantaneous reactions by bipolar patients while subjected to emotional stimuli such as IAPS and TAT images. Accordingly, in order to ensure the reliability of the proposed approach and avoid false positive findings, further studies will consider a higher number of patients. We will also explore additional aspects of the linear and nonlinear identification as related to depression/bipolar states. Moreover, we will explore more carefully the physiological meaning of the dynamic autonomic signatures both in the context of the underlying mood state, and as a result of the different stimuli administered within the dedicated protocol. Our approach will be also further extended to the wider framework of the PSYCHE project [3, 21–24], which considers several other variables (e.g. voice, activity index, sleep pattern alteration, electrodermal response, biochemical markers).

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