Temporal Trends of Neuro-Autonomic Complexity during Severe Episodes of Bipolar Disorders

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***Abstract*— Bipolar disorder is a chronic psychiatric condition during which patients experience mood swings among depression, hypomania or mania, mixed state (depression-hypomania) and euthymia, i.e., good affective balance. Nowadays, an objective characterization of the temporal trends of the disease as a response to the pharmacological treatment through physiological signatures, especially during severe episodes, is still missing. In this study we show interesting findings relating neuro-autonomic complexity to severe pathological mood states. More specifically, we studied Sample Entropy (SampEn) measures on Heart Rate Variability series gathered from four bipolar patients recruited within the frame of the European project PSYCHE. Patients were monitored through long term ECG recordings from the first hospital admission until clinical remission, i.e., the euthymic state. We observed that a mood transition from mixed-state to euthymia passing through depression can be characterized by increased SampEn values, i.e. as the patient is going to recover, SampEn increases. These results are in agreement with the current literature reporting on the complexity dynamics of the cardiovascular system and can provide a promising and viable clinical decision support to objectify the diagnosis and improve the management of psychiatric disorders.**

I. Introduction

Bipolar Disorder (BD) is a chronic psychiatric condition recognized to be one of the most common and dangerous disorder of the affectivity [1]. People affected by BD manifest drastically altered mood regulation, experiencing unbalanced mood shifts among depression, mania or hypomania, and mixed states (both depression and hypomania), thus having a significant impact on patients' social, occupational, and general functioning and wellbeing. Depression is characterized by sadness and hopelessness (including suicidal ideation), whereas mania leads to euphoria or irritability, excessive energy, hyperactivity, hypertrophic self-esteem, and reduction of sleeping need. The moderate form of mania is called hypomania. Sometimes, bipolar patients exhibit symptoms from both the two clinical states at the same time (e.g. simultaneous presence of hyperactivity and lack of sleep needing with feeling of sadness and suicidal thoughts). This status is defined as mixed state. Finally, periods in which patients do not show any pathological signs are called euthymic states. It is important also to underline that mood disorders diagnosis and evaluation (e.g., severity assessment) is based on clinical interviews and questionnaires. Although these methods are well standardized and provide a high reproducibility and accuracy a biological, an objective diagnostic exam (i.e., an external diagnosis and severity assessment) is still missing.

Over the last few years, several studies have been focusing on changes in the Autonomic Nervous System (ANS) activity as possible source of biomarkers of pathological mood swings [2]–[8]. In particular, measures of Heart Rate Variability (HRV) series defined in the time and frequency domain as well as derived from the theory of nonlinear and complex systems, have been quite successful in characterizing patients with mental disorders with respect to healthy subjects [4], [8].

In previous methodological studies [9], [10], we provided evidences on how a multi-parametric data-mining approach, based on heartbeat dynamics over long term observations, can be profitably used to discern different pathological mood states associated to BD. Then, we showed how to significantly improve the assessment of patients with BD when methods and parameters related to the ANS linear and nonlinear dynamics take into account the information related to the temporal transition among mood states [11]–[13]. Here, we investigate how to characterize the response to treatment on a particular kind of BD patients who show severe symptoms during depression and mixed-state episodes. In particular, we investigated the actual existence of a temporal trend in ANS complexity through a widely used complexity measure such as the Sample Entropy [14], estimated on long-term HRV series gathered from four patients.

Nonlinear dynamics of cardiovascular variability, in fact, has been widely recognized in the current literature as a result of many complex interaction between the sympathetic and parasympathetic control of heart rate [15], showing also multifractal properties [16]–[18] and being affected by emotional stimuli [19]–[22], aging [23], [24], and disease [25]–[28].

Data used in this study was gathered within the frame of the European project PSYCHE (Personalized monitoring SYstems for Care in mental HEalth) [10]–[12], [21], whose ambitious objective was the development of a novel personalized multi-parametric platform comprised of a wearable monitoring system including embedded sensors and a smartphone to better manage patients affected by mental disorders such as BD.

II. Materials and Methods

A. The PSYCHE Monitoring System

Extensive details on the PSYCHE project and the PSYCHE system can be found in [10]–[12]. Here, we used data collected through the PSYCHE monitoring system which is mainly comprised of a sensorized t-shirt able to acquire

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Fig. 1. Sensorized t-shirt as the core of the PSYCHE Wearable monitoring system

ECG-HRV, respiration activity (RSP), and movement activity including its classification (i.e. supine, sitting, sleep posture, etc.), see fig. 1. All mentioned physiological signals are acquired and preprocessed by means of a low-power electronic device which is embedded into the garment which was developed by Smartex s.r.l (Pisa, Italy). In this study, ECG signals were used to extract the HRV series, which are constituted by the distance of two consecutive R-peaks of the ECG. During the acquisition patients were free to execute their daily activities and the signals were stored in a microSD card and then sent to a central server through a smartphone for further analysis.

B. Patient Recruitment and Experimental Protocol

Four patients (one male, age ranged from 32 to 58) were recruited in the Psychiatric clinical ward at the Pisa University Hospital according to the following exclusion / inclusion criteria:

- age between 18-65 years
- clinical diagnosis of bipolar disorder and of acute mood episode
- absence of high risk suicidal behaviors
- change of treatment (dosage and/or drugs) within the previous two weeks
- absence of delusions and hallucination
- absence of a conduct abuse disorders
- possibility to express informed consent to the study

Patients were studied with an average frequency of 2-3 times a month. Patients were monitored during an acute episode of BD and followed until reaching clinical remission, i.e., until the reaching of an euthymic state as long as such a condition was presented within 3 months after the first visit. In any case, in this study no more than six evaluations per patient were performed. All clinical states were evaluated by clinicians according to DSM-IV-TR criteria. In this study, we recruited acutely depressed and depressed/hypomanic, hospitalized patients. Table I shows the details on the patients gender, age, and mood states during the course of the disease.

Pharmacological treatments included antidepressant, mood stabilized, or antipsychotic.

TABLE I PATIENTS CHARACTERISTICS

Patients	Age	Gender	Visit number				
			1	2	3	4	5
BP1	52	F	dep	dep	euth		
BP2	45	F	dep	dep	dep	euth	euth
BP3	58	M	mix	mix	dep	euth	
BP4	32	F	mix	mix	euth		

dep:depression, mix: mixed episode, euth: euthymic state.

In line with literature, we considered the patient in a depressed status when QIDS-C16 score was >8 a maniac/hypomaniac status when YMRS was score >6 and a mixed episode when the two scales were both over the above-mentioned cut-off threshold.

Before the recruitment, a professional clinician explained the rationale of the study and all the subjects read and signed the informed consent document. Patients were asked to wear the PSYCHE wearable monitoring system at all times until the battery ran out, i.e. approximately 18 hours. Therefore, there was no need of particular experimental conditions as the patient was free to perform normal activities. The study was approved by the ethical committee of the Pisa University Hospital "Santa Chiara", Italy.

C. Methodology of Signal Processing

The ECG signals were acquired with a sampling rate of 250 Hz and pre-filtered through a tenth order band-pass finite impulse response filter having cut-off frequencies of 0.05-35 Hz, approximated by the Butterworth polynomial. Afterwards, R-waves were automatically recognized by applying the Pan-Tompkins [29] algorithm to the longest artifact-free segments and then considered for further analysis.

We performed SampEn estimations on artifact-free RR interval series gathered from long term recordings from each visit of each patient. Such segments lasted for no more than 5 hours. SampEn [14] refers to the calculation of the so-called Approximate Entropy, which was defined for the calculation on short and noisy time series [30].

The algorithm considers discrete time series $u(1), u(2), ..., u(N)$ to define the vectors $x(1), x(2), ..., x(N-m+1)$ defined in $\mathbb{R}^m$ through $x(i) = [u(i), u(i+1), ..., u(i+m-1)]$. Then, the distance between two vectors x_i and x_j is defined according to the Takens formulation :

$$d[x(i), x(j)] = max_{k=1,2,...,m}|u(i+k-1) - u(j+k-1)| \quad (1)$$

For each i, with $1 \leq i \leq N-m+1$, we measured a parameter $C_i^m(r)$:

$$C_i^m(r) = \frac{\text{Number of j such that}(d[x(i), x(j)] \leq r)}{N-m+1} \quad (2)$$

and defined:

$$C^m(r) = \frac{\sum_{i=1}^{N-m+1} \log C_i^m(r)}{N-m+1} \quad (3)$$

This value measures the frequency at which the vectors of length m, considered as neighbors, remain within a sphere of radius r even if the dimension of pattern increases from m to $m+1$.

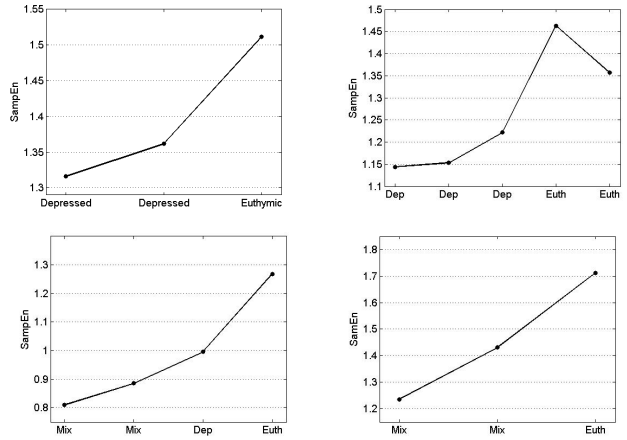

Fig. 2. Temporal trends of SampEn for HRV signals of bipolar subject: BP1 (top-left), BP2 (top-right), BP3 (bottom left),BP4 (bottom right). Dep=depressed; Euth=euthymic; Mix=mixed state.

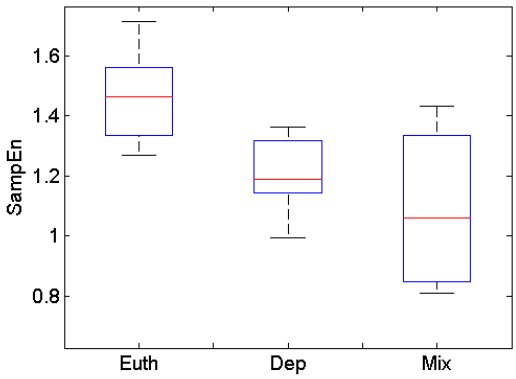

Fig. 3. Box-plots of SampEn values for the three mood states (Mix=mixed state; Dep=depressed; Euth=euthymic)

$SampEn$ is finally calculated by the expression [14].

$$\text{SampEn(m,r)} = -\ln \frac{C^{m+1}(r)}{C^{m}(r)} \tag{4}$$

In our study we used $r = 0.20 * std$ and $m = 2$, where std refers to the standard deviation of time series, as suggested by previous studies [14].

III. Experimental Results

We computed the SampEn complexity measure associated to each visit/acquisition of each patient. SampEn values and their graphical trends are shown in Table II and Fig. 2, respectively.

TABLE II SampEn values associated to BP patients under study

Patient	Acq.1	Acq.2	Acq.3	Acq.4	Acq.5
BP1	1.31	1.36	1.51		
BP2	1.14	1.15	1.22	1.46	1.35
BP3	0.81	0.88	0.99	1.27	
BP4	1.24	1.42	1.71		

Each patient shows an increasing trend of the SampEn consistently with the improvement of the mood state, going from severe depressed or mixed state (usually at the study entry visit) to euthymic state, i.e. the remission. It is worthwhile that the trend of all the patients is always increasingly although the first two or three (in BP2 case) acquisitions exhibit the same clinical label. This behavior supports the hypothesis that when the sample entropy is going to grow over the acquisitions, then the patient is getting better in terms of psychiatric symptoms, i.e. he is going towards euthymia.

In order to investigate the differences in SampEn values among all the patients, we further performed an inter-subject statistical analysis aimed at discerning the three mood states as euthymic, depressed, and mixed. Due to the low number of samples belonging to each clinical state, such a statistical evaluation was performed by means of the Kruskal-Wallis non-parametric test without using the Chi-square approximation. As a results, a probability $p < 0.05$ was associated to the null hypothesis of non-equal median among the three mood states. A further post-hoc analysis, performed through the Mann-Whitney test, revealed significant differences between the euthymic and both the depressed and mixed state ($p < 0.05$). Box plot statistics are shown in Fig. 3.

IV. Discussion and Conclusion

In this study, we investigated trends of neuro-autonomic complexity gathered from four bipolar patients through SampEn values, estimated on long term HRV series. Patients presented severe mood disorder episodes and underwent pharmacological treatments until remission, i.e., until reaching a good affective balance.

Through the PSYCHE system and the related long term recordings of ANS signals, it was possible to extract and analyze simple but effective complex measures such as the SampEn.

We found a consistent increasing trend of SampEn on each of the four patients during mood transitions from mixed-state to euthymia passing through depression, or from depression to euthymia. Therefore, it is possible to hypothesize that the nonlinear dynamics of the complex ANS control on the cardiovascular system is affected by the mood state of bipolar patients. Although the number of patients involved in this study is low, the experimental results are of strong interest and they are in agreement with the current literature reporting how higher complexity is often associated to healthier physiological processes. As an example, it has been shown that significantly lower SampEn values, computed on HRV series, are associated to depressed states with respect to healthy subjects [4]. As a matter of fact, in our study the mixed state, which can be considered as the one of the most severe state of BD, was associated to the lowest SampEn values when compared to the depressed and euthymic states [23], [24], [31]. Furthermore, the inter subject analysis suggested that the euthymic state, when compared to the other pathological mood states of BD, can be associated to a higher average complexity level and to a limited inter-subject variability.

From a clinical perspective, if confirmed by a larger number of patients, these findings would greatly improve the treatment assessment in mental care as ineffective treatments would be changed very quickly and profitably. Moreover, it

would be possible to hypothesize that if a significant number of acquisitions would be available on a given patient, then simple prediction approaches based on linear or nonlinear combinations of previous acquisitions could be implemented in order to forecast the future states.

It is important to underline that forecasting the response to psychiatric treatments is widely recognized to be one of the major clinical problem. Even if appropriate drugs are administered, a relatively large number of patients do not respond and there are a few indicators, at the beginning of the treatment that allow physicians to predict whether their medical prescription will work or not. Thus, clinicians often need to try and adjust their treatments if they realize that the expected clinical response is not coming.

Our future studies will progress to increasing the number of patients enrolled in order to confirm the reliability of the proposed approach, which will be also further extended within the frame of the PSYCHE project, including several other available variables (e.g voice, activity index, sleep pattern alteration, electrodermal response, biochemical markers).

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REFERENCES

[1] K. Merikangas *et al.*, "Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative," *Archives of general psychiatry*, vol. 68, no. 3, p. 241, 2011.

[2] G. Iverson *et al.*, "A new potential marker for abnormal cardiac physiology in depression," *Journal of behavioral medicine*, vol. 28, no. 6, pp. 507–511, 2005.

[3] R. M. Carney, K. E. Freedland, and R. C. Veith, "Depression, the autonomic nervous system, and coronary heart disease," *Psychosomatic medicine*, vol. 67, no. Supplement 1, pp. S29–S33, 2005.

[4] S. J. Leistedt, P. Linkowski, J. Lanquart, J. Mietus, R. B. Davis, A. L. Goldberger, and M. D. Costa, "Decreased neuroautonomic complexity in men during an acute major depressive episode: analysis of heart rate dynamics," *Translational psychiatry*, vol. 1, no. 7, p. e27, 2011.

[5] A. A. Weinstein, P. A. Deuster, and W. J. Kop, "Heart rate variability as a predictor of negative mood symptoms induced by exercise withdrawal." *Medicine and science in sports and exercise*, vol. 39, no. 4, pp. 735–741, 2007.

[6] B. L. Henry, A. Minassian, M. P. Paulus, M. A. Geyer, and W. Perry, "Heart rate variability in bipolar mania and schizophrenia," *Journal of psychiatric research*, vol. 44, no. 3, pp. 168–176, 2010.

[7] A. Voss *et al.*, "Linear and nonlinear methods for analyses of cardiovascular variability in bipolar disorders," *Bipolar disorders*, vol. 8, no. 5p1, pp. 441–452, 2006.

[8] H. Cohen, Z. Kaplan, M. Kotler, I. Mittelman, Y. Osher, and Y. Bersudsky, "Impaired heart rate variability in euthymic bipolar patients," *Bipolar Disorders*, vol. 5, no. 2, pp. 138–143, 2003.

[9] G. Valenza and E. P. Scilingo, "Autonomic nervous system dynamics for mood and emotional-state recognition: Significant advances in data acquisition, signal processing and classification," 2013.

[10] G. Valenza, C. Gentili, A. Lanatà, and E. P. Scilingo, "Mood recognition in bipolar patients through the psyche platform: Preliminary evaluations and perspectives," *Artificial intelligence in medicine*, vol. 57, no. 1, pp. 49–58, 2013.

[11] A. Greco, A. Lanata, G. Valenza, G. Rota, N. Vanello, and E. Scilingo, "On the deconvolution analysis of electrodermal activity in bipolar patients," in *Proceeding of IEEE-EMBC*. IEEE, 2012, pp. 6691–6694.

[12] G. Valenza, M. Nardelli, A. Lanata, C. Gentili, G. Bertschy, R. Paradiso, and E. Scilingo, "Wearable monitoring for mood recognition in bipolar disorder based on history-dependent long-term heart rate variability analysis," *IEEE Journal of Biomedical and Health Informatics*, in press.

[13] A. Greco, G. Valenza, A. Lanata, G. Rota, and E. Scilingo, "Electrodermal activity in bipolar patients during affective elicitation," *IEEE Journal of Biomedical and Health Informatics*, 2014.

[14] J. Richman and J. Moorman, "Physiological time-series analysis using approximate entropy and sample entropy," *American Journal of Physiology- Heart and Circulatory Physiology*, vol. 278, no. 6, p. H2039, 2000.

[15] K. Sunagawa, T. Kawada, and T. Nakahara, "Dynamic nonlinear vagosympathetic interaction in regulating heart rate," *Heart and Vessels*, vol. 13, no. 4, pp. 157–174, 1998.

[16] L. Glass, "Introduction to controversial topics in nonlinear science: Is the normal heart rate chaotic?" *Chaos: An Interdisciplinary Journal of Nonlinear Science*, vol. 19, no. 2, p. 028501, 2009.

[17] P. C. Ivanov, L. A. N. Amaral, A. L. Goldberger, S. Havlin, M. G. Rosenblum, Z. R. Struzik, and H. E. Stanley, "Multifractality in human heartbeat dynamics," *Nature*, vol. 399, no. 6735, pp. 461–465, 1999.

[18] A. L. Goldberger, "Nonlinear dynamics, fractals and chaos: applications to cardiac electrophysiology," *Annals of biomedical engineering*, vol. 18, no. 2, pp. 195–198, 1990.

[19] G. Valenza, A. Lanata, and E. P. Scilingo, "The role of nonlinear dynamics in affective valence and arousal recognition," *Affective Computing, IEEE Transactions on*, vol. 3, no. 2, pp. 237–249, 2012.

[20] G. Valenza, A. Lanatá, and E. P. Scilingo, "Improving emotion recognition systems by embedding cardiorespiratory coupling," *Physiological measurement*, vol. 34, no. 4, p. 449, 2013.

[21] G. Valenza, L. Citi, C. Gentili, A. Lanata, E. Scilingo, and R. Barbieri, "Characterization of depressive states in bipolar patients using wearable textile technology and instantaneous heart rate variability assessment," *IEEE Journal of Biomedical and Health Informatics*, 2014.

[22] G. Valenza, L. Citi, A. Lanatá, E. P. Scilingo, and R. Barbieri, "Revealing real-time emotional responses: a personalized assessment based on heartbeat dynamics," *Nature Scientific reports*, vol. 4, 2014.

[23] A. I. Batchinsky, W. H. Cooke, T. Kuusela, and L. C. Cancio, "Loss of complexity characterizes the heart rate response to experimental hemorrhagic shock in swine*," *Critical care medicine*, vol. 35, no. 2, pp. 519–525, 2007.

[24] L. A. Lipsitz, "Physiological complexity, aging, and the path to frailty," *Science's SAGE KE*, vol. 2004, no. 16, p. pe16, 2004.

[25] C. Poon and C. Merrill, "Decrease of cardiac chaos in congestive heart failure," *Nature*, vol. 389, no. 6650, pp. 492–495, 1997.

[26] G. Valenza, L. Citi, and R. Barbieri, "Instantaneous nonlinear assessment of complex cardiovascular dynamics by laguerre-volterra point process models," in *Proceedings of IEEE-EMBC*. IEEE, 2013.

[27] D.-G. Shin, C.-S. Yoo, S.-H. Yi, J.-H. Bae, Y.-J. Kim, J.-S. Park, and G.-R. Hong, "Prediction of paroxysmal atrial fibrillation using nonlinear analysis of the rr interval dynamics before the spontaneous onset of atrial fibrillation." *Circulation journal: official journal of the Japanese Circulation Society*, vol. 70, no. 1, p. 94, 2006.

[28] G. Valenza, L. Citi, E. P. Scilingo, and R. Barbieri, "Inhomogeneous point-process entropy: An instantaneous measure of complexity in discrete systems," *Physical Review E*, vol. 89, no. 5, p. 052803, 2014.

[29] J. Pan and W. J. Tompkins, "A real-time qrs detection algorithm," *Biomedical Engineering, IEEE Transactions on*, no. 3, pp. 230–236, 1985.

[30] S. Pincus, "Approximate entropy as a measure of system complexity," *Proceedings of the National Academy of Sciences*, vol. 88, no. 6, p. 2297, 1991.

[31] L. A. Lipsitz, J. Mietus, G. B. Moody, and A. L. Goldberger, "Spectral characteristics of heart rate variability before and during postural tilt. relations to aging and risk of syncope." *Circulation*, vol. 81, no. 6, pp. 1803–1810, 1990.