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LETTER

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Mood states modulate complexity in heartbeat dynamics: A multiscale entropy analysis

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Abstract – This paper demonstrates that heartbeat complex dynamics is modulated by different pathological mental states. Multiscale entropy analysis was performed on R-R interval series gathered from the electrocardiogram of eight bipolar patients who exhibited mood states among depression, hypomania, and euthymia, *i.e.*, good affective balance. Three different methodologies for the choice of the sample entropy radius value were also compared. We show that the complexity level can be used as a marker of mental states being able to discriminate among the three pathological mood states, suggesting to use heartbeat complexity as a more objective clinical biomarker for mental disorders.

Introduction. – Nonlinear analysis of human physiological signals has been widely recognized to provide relevant information on psychophysiological and pathological states [1]. Many physiological processes, in fact, involve nonlinear frequency modulation or multifeedback interactions associated to long-range correlations [2,3]. Accordingly, many evidences in the literature on nonlinear dynamics of physiological signals show that complexity is a marker of health status of biological systems, and it is modulated by external stimuli, aging and presence of disease [1,3–9].

A paradigmatic application of this methodological approach is given by the cardiovascular control dynamics, mediated by the Autonomic Nervous System (ANS). This system is very often investigated through the analysis of the series obtained by the time intervals between two consecutive R-waves detected from the electrocardiogram, *i.e.* the R-R intervals, whose variability is defined as Heart Rate Variability (HRV). In the last decades, HRV studies using both linear and nonlinear modeling have been characterizing the influence of the ANS on the heartbeat, revealing the various nonlinear neural interactions and integrations occurring at the sinoatrial node and receptor levels [10]. Such phenomena include multiscale and fractal properties and much of nonlinear and non-stationary dynamics analysis provides significant cues for diagnostic and prognostic use [3,4].

Among others, MultiScale Entropy (MSE) is a powerful tool to quantify the nonlinear information of a time series over multiple time scales [11] through sample entropy (SampEn) [12] algorithms. In the literature it can be found that MSE analysis has been applied to characterize human gait dynamics [13], Alzheimer's disease through EEG signals [14], drug-naive schizophrenia [15] and autism spectrum conditions [16]. Recently, MSE has been also applied to HRV data to study patients with type 1 diabetes mellitus [17] or with aortic stenosis subjects [18], effects of orthostatic stress [19]. Other studies involving healthy subjects point out some typical behaviors of MSE: entropy increases from small to large scales and then stabilizes its value at constant values; in patients with arrhythmia, the entropy decreases and then remains constant; in patients with congestive heart failure, the entropy decreases at the beginning and then gradually increases [11].

A recent frontier of nonlinear analysis on HRV data is represented by the assessment of psychiatric disorders. Most of the known mental disorders, in fact, are currently diagnosed relying on the clinicians' experience, who is supported only by verbal interviews and scores from specific questionnaires. Moreover, mental assessment

through non-invasive, easy-to-record, and robust series such as HRV could open dramatic clinical perspectives in objectively managing the illness, helping patients, facilitating the interaction between patient and physician as well as to alert professionals in case of critical pathological episodes. In this study, we describe how to effectively characterize different pathological mental states using MSE analysis of HRV series gathered from bipolar patients. Bipolar disorder can be described as an illness in which patients experience depressive or maniacal states. 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. Periods in which patients do not show any pathological signs are called euthymic states.

We have been inspired by several works relating ANS marker to depression [20–24]. In a previous work [25] it has been shown that linear-derived parameters are inadequate to discern healthy subjects and patients with major depressive disorder as they have a variance as high as to not be able to infer an appreciable difference between the two groups, so only intra-subject evaluations have been possible. On the contrary, nonlinear measures such as MSE allowed the discrimination of depressive patients and healthy subjects always showing a significant decrease of the complexity in the pathological group [26,27]. Accordingly, in this work we hypothesize that MSE analysis on HRV series gathered from bipolar patients can provide information about the clinical mood state. Moreover, we investigate whether this analysis is able to perform an inter-subject analysis, distinguishing among three different pathological mental states, *i.e.* depression, hypomania, and euthymia. As methodological contribution, we exploit three different approaches by choosing the most fundamental and sensible parameter of MSE analysis: the radius of the sample entropy. Long-term night monitoring was performed using *ad hoc* wearable monitoring systems developed in the framework of the European project PSYCHE (Personalized monitoring SYstems for Care in mental HEalth), whose details are reported in [25,28].

Materials and methods. –

Experimental protocol. Next, we briefly describe the recruitment of eligible subjects, the experimental protocol, and data acquisition, whose details are reported in [25,28]. We analyzed the nonlinear heartbeat dynamics of 8 bipolar patients selected according to the following features: age between 18 and 65, presence of a mood state between depressive and hypomanic at the moment of the recruitment, low risk of suicidality (as assessed as no thoughts of death and no previous attempts), no somatic or neurologic disorders that might be related to bipolar disorders (*e.g.* thyroid alterations), absence of cognitive impairment, absence of substance abuse disorders, necessity of a change in treatment (treatment change is defined as a augmentation of doses, introduction of or switch to other drugs, introduction of physical treatments), all the patients will sign the informed consent for the PSYCHE project already approved by the Ethical Committee of Strasbourg. The protocol planned a study entry visit when the patient was experiencing a depressive or hypomanic phase. Patients were studied with an average frequency of 2–3 times a month. Each patient was evaluated and monitored from the day of the hospital admission toward 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. Accordingly, we analyzed a total amount of 16 night recordings, 6 out of which were associated to the label depression, 5 to label hypomania, and 5 to label euthymia. All clinical states have been evaluated according DSM-IV-TR criteria [29] and all patients were recruited in the out-patient University clinic of Strasbourg, France. The PSYCHE wearable system has been given to the patients in the afternoon and recollected the morning after. HRV data were collected from each acquisition of each patient using the core system of the PSYCHE wearable monitoring platform. It consists in a comfortable, textile-based sensorized T-shirt developed by Smartex s.r.l., embedded with electrodes which are able to acquire electrocardiogram (ECG), from which the HRV signals are extracted after *ad hoc* pre-processing and R-peak extraction steps [25,28]. During all the acquisitions, the ECG sampling frequency was set to 250 Hz.

Multiscale entropy (MSE) methodology and influence of the r parameter. Concerning the analysis, first we briefly describe the theory behind the MSE methodology emphasizing the issue of choosing the optimal value of the SampEn radius. MSE is based on the calculation of the SampEn over several time series, which are constructed from the original discrete time series by averaging the data points within non-overlapping windows of increasing length, τ. Formally, given a time series $\{x_1, \ldots, x_i, \ldots, x_N\}$ and a scale factor τ, each element of a course-grained series $\left\{y^{(\tau)}\right\}$ is calculated as $y_j^{(\tau)} = \frac{1}{\tau}\sum_{i=(j-1)\tau+1}^{j\tau} x_i, 1 \leq j \leq N/\tau$ and, for each of the series, $y_j^{(\tau)}$, SampEn is computed as suggested by [12,30]. SampEn estimation on each series starts with the calculation of the distance between two vectors x_1 and x_j on the phase space $x(1), x(2), \ldots, x(N-m+1)$, which is defined in $\mathbb{R}^m$, where $m \leq N$ is a positive integer associated to the embedding dimension of the series [31,32]. Then, all the distances within a radius r are counted and normalized by the quantity $N-m+1$. This procedure is performed twice considering the chosen value of m and $m+1$.

Therefore, two parameters are mainly involved in the MSE estimation: the embedding dimension m of the series [31,32], and r, a positive real number representing the margin of tolerance, *i.e.*, the radius. Previous studies suggest a fixed straightforward choice of the parameters

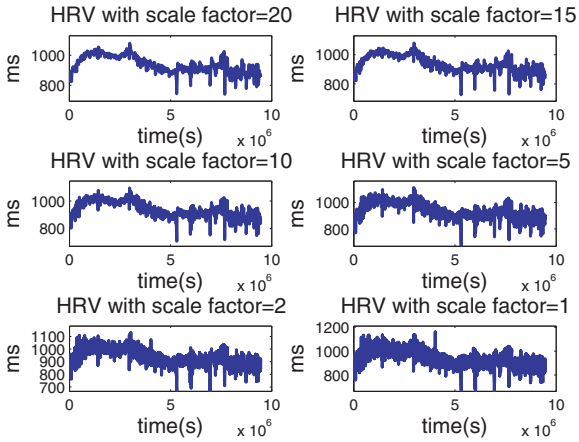

Fig. 1: (Colour on-line) Heartbeat dynamics gathered from a representative patient while experiencing the pathological mental state such as hypomania.

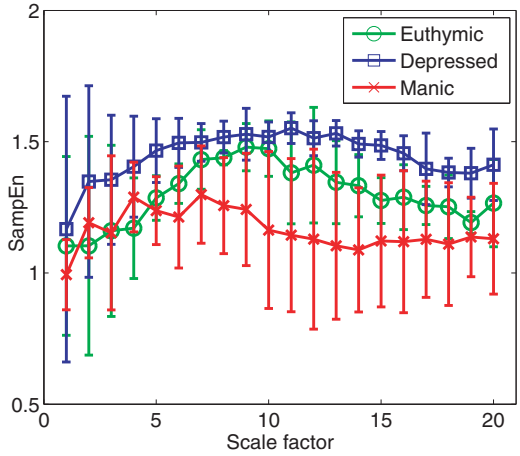

Fig. 2: (Colour on-line) MSE of heart rate dynamics in nocturnal period with Method I, values are expressed as median ± MAD.

as $m = 2$, and $r = 0.15\,\sigma$ where σ is the standard deviation of the series [11]. While such a choice could be reasonable for the m values, it could be pretty hazardous for the r value. Inter-subject variability, in fact, can lead to non-effective results whether the parameters involved in the analysis are not adaptive and personalized. Moreover, some researchers recently pointed out that the recommended r does not fit all situations and may lead to wrong results [33–35].

Therefore, in order to study the influence of the r value on the MSE estimation and to improve the objectivity of the experimental results, we tested three r-choosing methodologies:

MSE-Method I consists in the previously mentioned traditional choice for physiological data of $r = 0.15\,\sigma$ [13,27] evaluated for each acquisition of each subject.

MSE-Method II considers the *grouped* standard deviation of the series belonging to all patients [36,37]. Such a series is obtained by concatenation of the series of each acquisition/mood state.

MSE-Method III considers different r values for each acquisition of each subject so as to maximize the calculation of the Approximate Entropy ($ApEn$) [30] in the range $0.01\sigma \leq r \leq 1.2\sigma$ [33–35,38–43]. This popular method considers that the highest value $ApEn(r_k)$ is interpolated with the preceding and the following values, $ApEn(r_{k-1})$ and $ApEn(r_{k+1})$, with a parabola. The position of the vertex of the parabola gives r_{max}.

It is straightforward to notice that the MSE-Method III ensures a more objective selection of the r value than the previous two methods. As both methodological and clinical advances, in this paper we investigated all the three mentioned methods on the MSE estimation to replicate the previous findings on the complexity changes in psychopathologies [26,27], looking for complexity modulations among different mood/mental states.

On all the analysis, Kruskal-Wallis non-parametric tests were used to test the null hypothesis of having no statistical difference in complexity indices among patients acquisition groups (euthymic, depressed, hypomanic). Mann-Whitney non-parametric U-tests were used to compare two samples belonging to two different groups on the *post hoc* statistical analysis. The use of such non-parametric tests is justified by having non-Gaussian distribution of the samples ($p < 0.05$ given by the Shapiro-Wilk test having the null hypothesis of Gaussian-distributed samples).

Results. – MSE, estimating up to the twentieth scale factor, was calculated on the longest segment of consecutive artifact-free samples of each acquisition of each patient. Such a longest HRV series lasted for no less than 53 minutes and no more than 4 hours and 24 minutes. All results are expressed as median and its respective absolute deviation (*i.e.* for a feature X, $X = \text{Median}(X) \pm \text{MAD}(X)$ where $\text{MAD}(X) = \text{Median}(|X - \text{Median}(X)|)$). The m value is fixed for all cases to the standard value $m = 2$. Experimental results on using the MSE methods follow below. Figure 1 shows the HRV data for a representative patient while experiencing hypomania.

MSE-Method I. This method uses $r = 15\,\sigma$, where σ is the standard deviation of each HRV series, for the MSE calculation. The Kruskal-Wallis non-parametric test showed no statistical difference among the three pathological groups ($p > 0.05$). Figure 2 shows the MSE results over all the scale factors.

MSE-Method II. This method chooses the radius as 15% of the standard deviation of all series. Likewise the previous method, the Kruskal-Wallis non-parametric test showed no statistical difference among the three pathological mental states ($p > 0.05$). Figure 3 shows the MSE results over all the scale factors.

MSE-Method III. This method searches the objective r_{max} value which maximizes $ApEn$ of each HRV series. We found that the maximum value of entropy was always within the range from 0.001σ to 0.30σ. The Kruskal-Wallis

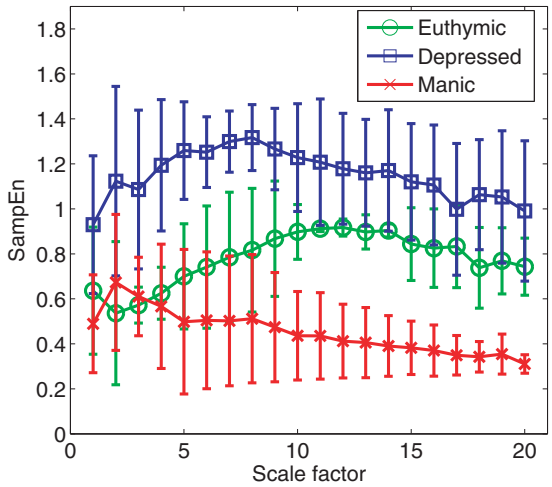

Fig. 3: (Colour on-line) MSE of heart rate dynamics in nocturnal period with Method II, values are expressed as median ± MAD.

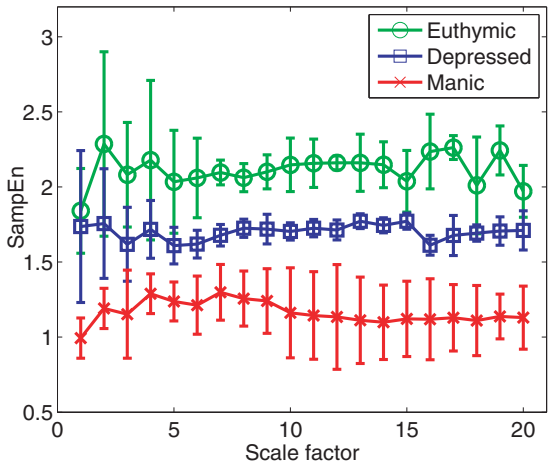

Fig. 4: (Colour on-line) MSE of heart rate dynamics in nocturnal period with Method III, values are expressed as median ± MAD.

Table 1: CI values estimated from the MSE analysis of HRV series gathered during nocturnal recordings. Values are expressed as median and its respective absolute deviation.

	Short time	Higher time
Euthymic	15.18 ± 3.85	38.11 ± 2.40
Depressed	11.71 ± 1.50	31.39 ± 3.26
Hypomanic	9.14 ± 1.18	22.17 ± 4.17

test revealed statistical differences between the groups at all scales. In particular, when scale is equal to 1 and for scale values comprised between 7 and 19, the null hypothesis of having no difference was rejected with $p < 0.01$. At scales 2, 3, 4 and 6 the null hypothesis was rejected with $p < 0.05$, while at the remaining scale 5, the obtained p value is less than 0.06. Moreover, the *post hoc* analysis, performed using the Tukey procedure for the correction of the statistical significance, showed significant differences between the hypomanic and euthymic states with ($p < 0.05$) at scales 1,2 and from 4 to 20. At scales 1,9,10 hypomanic group data was also different from depressed. Figure 4 shows the MSE results over all the scale factors.

MSE - Complexity Index Analysis. As a complementary feature, we evaluated the Complexity Index (CI) [27] of each series as the area under the curve of the MSE graph. CI is calculated on short time scales, from 1 to 8, and on higher time scales, from 1 to 20. Results of the CI index, referring to the best MSE estimations which are given by the MSE-Method III, are shown in table 1 for the three considered pathological mental states (euthymic, depressed, hypomanic). The Kruskal-Wallis test revealed statistical differences between the three mood states on both short ($p < 0.03$) and higher time scales ($p < 0.001$). Concerning the *post hoc* analysis, also performed using the Tukey correction, the depressive group showed statistical difference with respect to the hypomanic group ($p < 0.02$) on short time scales, whereas significant variations were found between the hypomanic and euthymic states on both short and higher time scales ($p < 0.03$). It is worthwhile noting that the CI results are not biased by significant changes of the chosen r values of each considered recording. As a matter of fact, the following r_{max} statistics were found: 0.0024 ± 0.0012 seconds for the manic state, 0.0032 ± 0.0014 seconds for the euthymic state, 0.0023 ± 0.0006 seconds for the depressed. A probability of 0.4252 was associated to the null hypothesis of having no difference among the three mood states, according to the Kruskal-Wallis non-parametric test.

Complementary analyses. In order to further investigate how heartbeat dynamics is modulated during different pathological mental states, a multiscale Detrended Fluctuation Analysis (mDFA) was applied. According to the MSE processing, the mDFA, estimating up to the twentieth scale factor, was calculated on the longest segment of consecutive artifact-free samples of each acquisition of each patient. On both α_1 and α_2 indices, the Kruskal-Wallis non-parametric test showed no statistical difference among the three pathological groups ($p > 0.05$) for each of the twenty scales. These results suggest that heartbeat dynamics displays similar long- and short-range correlations between different pathological mental states.

As mood states could be associated to changes in the sympatho-vagal balance of ANS, we also tested the null hypothesis that standard HRV parameters defined in the frequency domain, as the power in the Low-Frequency (LF) and High-Frequency (HF) bands along with their ratio, are significantly altered among the three pathological mood states. Earlier studies, in fact, have shown a significant change in complexity measures and in the DFA scaling behavior of HRV in response to sympathetic or parasympathetic activation due to rest and exercise [44], sleep-wake and sleep-stage transitions [45,46], circadian

phases [47], beta-blockers and atropine drug administration [48], aging [49,50]. By calculating the HRV power spectra within non-overlapped moving time windows of 5 minutes of length and averaging on each observation, we found that no statistical difference is associated to the LF, HF, and LF/HF indices different mood states, according to the Kruskal-Wallis non-parametric tests ($p > 0.05$). Concerning the aging effects, we report that a probability value of 0.435 (from the Kruskal-Wallis non-parametric test) is associated to the null hypothesis of having no significant difference in age among the pathological mood states.

Finally, in order to investigate whether the heartbeat complexity modulation is due to a loss of nonlinear properties of the cardiovascular system or changes in the parameters of the system (which would remain governed by nonlinear equations), we further applied an established time domain method [51] to the RR interval series in order to test the presence of nonlinearity among the different mood states, as suggested by [52,53]. The outcomes from the nonlinearity test demonstrate that all the considered long-term recordings are characterized by a relevant presence of nonlinearity, over all the considered states (with $p < 0.05$).

Conclusion. – We studied the complexity of the heartbeat dynamics in bipolar patients through MSE analysis of HRV series. The choice of such a specific analysis is justified by the fact that MSE has been proven a powerful tool in translational psychiatry discerning patients with major depressive syndrome from healthy subjects [27], in spite of a high inter-subject variability. In particular, significant lower complexity has been found in the depressive patients with respect to the healthy subjects. Accordingly, our experimental hypothesis was to extend the discerning capability of these analysis by studying multiple pathological mental states associated to mood states. Bipolar patients, in fact, experience different mood states among depression, hypomania, and euthymia, which is the good affective balance. We processed sixteen HRV series gathered from eight patients during night recordings by using a comfortable wearable monitoring system developed within the PSYCHE project [25,28]. The major methodological issue in estimating the SampEn of MSE over the scale factors, which involves the choice of the r value, has been deeply exploited comparing three different approaches.

Using the objective estimation given by the so-called MSE-Method III, which searches maximum ApEn values in a parabola interpolating values $0.01\sigma \leq r \leq 1.2\sigma$ [33–35,43], we found an interesting complexity modulation coherent with both the current literature and different mood states. We found that higher complexity at all scales is associated to the euthymic state, whereas the depressive and hypomanic states show decreased complexity values ($p < 0.01$). Moreover, the complementary mDFA analysis suggests that pathological mental states modulate the pattern of signal complexity throughout different time scales without affecting patterns of signal amplitude with changing time scale. The nonlinearity tests also suggest that a loss of nonlinearity does not occur in case of mood disorders, as previously observed in the presence of, *e.g.*, heart failure [54]. The HRV power spectral analysis also suggests that, although sympatho-vagal dynamics can be affected by pathological mental states, the inter-subject variability is too high to allow such changes to be revealed through a simple analysis in the frequency domain. From this point of view, the complexity analysis resulted to be a much more powerful tool. We also state that the differences in heartbeat complexity found among the three pathological mood states are not biased neither by the age of the patients enrolled in the study nor by the r_{max} values that are a function of the HRV standard deviation. As in the current clinical practice the diagnosis of mental disorders does not rely on objective psycho-physiological markers, in agreement with the outcomes of this study, it could be possible to exploit HRV complexity indices to give a viable support to the clinical decision. Our findings confirm the importance of nonlinear temporal patterns in mood recognition [26,27]. Although the detailed physiology behind the complex dynamics of heartbeat variations has not been completely clarified, previous studies suggest that β-adrenoceptor system has little involvement in the generation of nonlinear HRV whereas α-adrenoceptors strongly influence the scaling properties of the time series [55]. Moreover, cholinergic iper-driving also induces changes in the complexity measures such as the MSE complexity index (seen in rats) [55]. This study has been performed in the frame of the PSYCHE project, where a multidisciplinary and multiparametric analysis of bipolar disorder through the processing of several behavioral, biochemical, and electrophysiological variables has been carried out. Other key variables such as the postural sway can also be taken into account as suggested in [56]. Patient monitoring includes constant feedback which interests the physician and which supports the patient. The ultimate goal of the PSYCHE project is to provide the physician with a basis for a more precise diagnosis and possibly a prediction of an imminent change in mental state, indicated by an alteration of the studied parameters.

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