Maximal-Radius Multiscale Entropy of Cardiovascular Variability: a Promising Biomarker of Pathological Mood States in Bipolar Disorders

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***Abstract*— Complexity measures from Multiscale Entropy (MSE) analysis of cardiovascular variability may provide potential biomarkers of pathological mental states such as major depression. To this extent, in this study we investigate whether complexity of Heart Rate Variability (HRV) is also affected in mental disorders such as bipolar disorders (BD). As part of the European project PSYCHE, eight BD patients experiencing multiple pathological mood states among depression, hypomania, and euthymia (i.e., good affective balance) underwent long-term night recordings through a comfortable sensing t-shirt with integrated fabric electrodes and sensors. Standard radius, i.e., 20% of the HRV standard deviation, and a maximal-radius choice for the sample entropy estimation were compared along with a further multiscale Renyi Entropy analysis. We found that, despite the inter-subject variability, the maximal-radius MSE analysis is able to discern the considered pathological mental states of BD. As the current clinical practice in diagnosing BD is only based on verbal interviews and scores from specific questionnaires, these findings provide evidence on the possibility of using heartbeat complexity as the basis of novel clinical biomarkers of mental disorders.**

I. Introduction

Bipolar Disorder (BD) is one of the most common and dangerous chronic psychiatric condition during which patients can experience mood swings among depression, mania or hypomania, and mixed states comprised of both depressive and hypomaniac episodes [1]. Hypomania refers to a moderate form of mania, i.e. pathologic euphoria or irritability or excessive energy, whereas depression is related to sadness and hopelessness (including suicidal ideation). In addition, BD mood states are always characterized by comorbidity phenomena, i.e., simultaneous presence of symptoms which are shared with other psychiatric disorders. These pathological mood states alternate along the time, may be including periods of good affective balance called euthymia.

Clinical problems of BD are mainly related to its diagnosis. Current clinical practice, in fact, takes only into account interviews and scores from psychological questionnaires, physician own expertise in addition to patients' description of symptoms. Then, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) version IV-TR [2], the diagnosis of BD relies on the number of symptoms and clinical scores, hence likely leading to subjective interpretations, inconsistencies, and misdiagnoses [1], [3].

Recently, several studies proposed the use of Autonomic Nervous System (ANS) dynamics for the assessment of pathological mental states such as major depression [4]–[8], also highlighting complexity and nonlinear measures derived from the analysis of cardiovascular variability as an important element to distinguish psychophysiological and pathological states [4]–[18]. To this extent, this study aims at investigating whether complexity analysis of cardiovascular variability can provide effective biomarkers also in characterizing different pathological mental states of BD.

In particular, we have been inspired by several works relating MultiScale Entropy (MSE) measures [19] to depression [4]–[8], [20], [21]. Accordingly, we hypothesize that a multiscale complexity analysis of RR interval series gathered from patients with BD can provide information about the clinical mood state. We investigated whether this analysis is able to overcome the inter-subject variability while distinguishing among three different pathological mental states, i.e. depression, hypomania, and euthymia. Concerning the methodology, in addition to MSE analysis, further complexity measures derived from the Renyi entropy measures are taken into account: the Quadratic Sample Entropy (QSE) measure, which is an alternative approach for determining the complexity of a series of RR intervals and can be interpreted as a measure of gaussianity [22]. The Renyi entropy analysis here is also applied in a multiscale fashion, as in [23].

In estimating both MSE and multiscale QSE (mQSE), the proper selection of one of the most sensible parameter of a multiscale complexity analysis, i.e., the radius of the sample entropy, is carefully taken into account by comparing a standard (i.e., 20% of the HRV standard deviation [8], [19]) and a maximal-radius choice [24]–[27]. Data used in this study come from long-term night monitoring acquisitions 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 [13], [14].

II. Material and Methods

A. Experimental Protocol

Extensive details on the recruitment of eligible subjects, experimental protocol, and data acquisition are reported in [13], [14]. Briefly, we analyzed 16 long-term night recordings of HRV series gathered from 8 bipolar patients through a personalized wearable monitoring systems, which was developed in the framework of the European project PSYCHE (Personalized monitoring SYstems for Care in mental HEalth) [13], [14], [28]. The protocol planned a study

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entry visit when the patient was experiencing a depressive, hypomaniac, or mixed phase. Patients were studied with an average frequency of 2-3 times a month and were recruited at the University Clinic of Strasbourg, France. All clinical states were evaluated by clinicians according to DSM-IV-TR criteria [2].

Six recordings were associated to the label 'depression', 5 to the label 'hypomania', and 5 to the label 'euthymia'. For each patient, data analysis was performed on the longest artifact-free recording of each acquisition. Such a series lasted for no more than 4 hours and 24 minutes. The PSYCHE wearable system was given to the patients in the afternoon and taken back the morning after.

B. Multiscale entropy (MSE)

MSE has been widely recognized as a powerful method to quantify the nonlinear information of a time series over multiple time scales [19] through sample entropy (*SampEn*) [29] algorithms. The detailed theory behind the MSE methodology can be found in [19]. Briefly, 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 $\{x_1,...,x_i,...,x_N\}$ and a scale factor τ, each element of a course-grained series $\left\{y^{(\tau)}\right\}$ is calculated as:

$$y_j^{(\tau)} = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i \tag{1}$$

with $1 \leq j \leq N/\tau$. For each of the series $y_j^{(\tau)}$, *SampEn* [29] estimation starts with the calculation of the distance between two vectors x_1 and x_j on the phase space $x(1),x(2),...,x(N-m+1)$, which is defined in $\mathbb{R}^m$, where $m \leq N$ is a positive integer associated to the embedding dimension of the series. 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 $m+1$ [29].

C. Quadratic Sample Entropy

Quadratic Sample Entropy (*QSE*) [22] is a *SampEn* related measure that comes from the definition of the Renyi entropy. Specifically, the quantity $E[f(X)]$ is the starting point to compute Renyi Entropy R_q of order q defined as:

$$R_q(X) = \frac{1}{1-q} log(E[f(X)^{q-1}]) \tag{2}$$

when $q = 1$, the Renyi Entropy corresponds to Shannon Entropy, while if $q = 2$, $R_2(X)$ is called quadratic Renyi entropy rate. Then, it is possible to define the differential Renyi entropy rate, D_q, as the difference between the Renyi Entropy of the density of order $m+1$ and of order m:

$$D_{q,m} = R_q(X_{m+1}) - R_q(X_m) \tag{3}$$

where m corresponds to the embedding dimension. Of note, $D_{q,m}$ for q=2 corresponds to the *SampEn* [22]. Finally, the *QSE* is defined as:

$$QSE = D_{q,m} + log(2r)|_{q=2} = SampEn + log(2r) \tag{4}$$

In this study, QSE analysis is performed in a multiscale fashion using appropriate r-values as described in the following paragraph.

D. Choice of Standard and Maximal Radius Value

According to the MSE and QSE methodology, two parameters are mainly involved in their estimation process: the embedding dimension m of the series, 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 as $m = 2$, and $r = 0.15\ \sigma$ where σ is the standard deviation of the series [8], [19]. Nevertheless, the inter-subject variability can easily lead to non-effective results whether the parameters involved in the analysis are not objectively adaptive and personalized. The variability of the series, in fact, can be function of very slow trends (changes in the mean RR) that likely are not related to the complexity modulation by pathological mental state. This concept has been recently pointed out in [24], [25], [27]. Therefore, in order to study the influence of the r-value on the MSE and QSE estimation, and to improve the objectivity of the experimental results, in this study we tested the following two r-choosing methodologies:

r-Method I, which consists in the previous mentioned traditional choice for physiological data of $r = 0.15\ \sigma$ [8], [19] evaluated for each acquisition of each patient.

r-Method II, which 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 $0.01 \leq r \leq 1.2$, as suggested in [24]–[27]. This 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 the maximal radius r_{max}.

III. Results

We apply both *r-Method I* and *r-Method II* to the MSE and multiscale QSE (mQSE) estimation to characterize complexity changes in three BD psycho-pathological states. On all the analysis, Kruskal-Wallis non-parametric tests were used to test the null hypothesis of having no statistical difference in the complexity indices among the 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). 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 $\text{MAD}(X) = \text{Median}(|X - \text{Median}(X)|)$).

MSE and mQSE, estimating up to the twentieth scale factor, were calculated on the longest segment of consecutive artifact-free samples of each acquisition of each patient. The m value is fixed for all cases to the standard value $m = 2$.

r-Method-I: On the MSE and mQSE calculation, the Kruskal-Wallis non-parametric test showed no statistical difference among the three pathological groups ($p > 0.05$) over all the scale factors (see Figure 1).

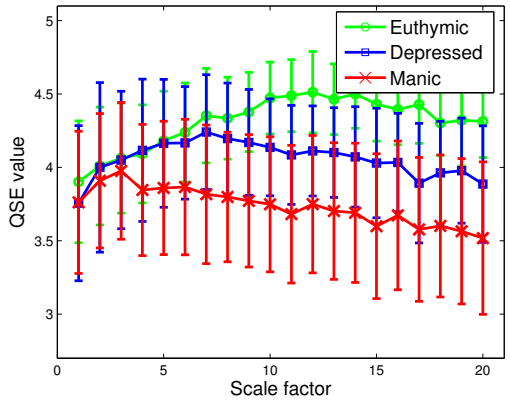

Fig. 1. Multiscale QSE analysis with $r = 0.15\sigma(RR)$ of heart rate dynamics in nocturnal period among mental states associated to pathological moods such as depression, hypomania, and euthymia. Values are expressed as $Median \pm MAD$.

r-Method-II: For this method, we found that the maximum value of entropy was always within the range from 0 to 0.30. Concerning the mQSE analysis, the Kruskal-Wallis non-parametric test showed no statistical difference among the three pathological mental states ($p > 0.05$) over all the scales. Concerning the MSE analysis, the Kruskal-Wallis 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 Bonferroni correction showed significant differences between the hypomanic and euthymic states with ($p < 0.05$) at scales 1, 2 and from 5 to 20. At scales 1,9,10 hypomanic group data was also different from depressed. The euthymic state was always associated to the highest complexity, followed by the depressive and hypomanic states, respectively.

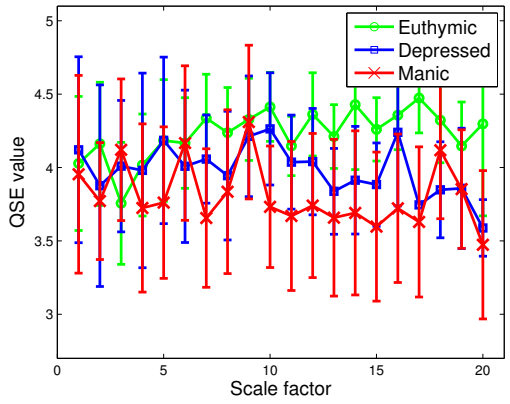

Fig. 2. Multiscale QSE analysis of heart rate dynamics in nocturnal period among mental states associated to pathological moods such as depression, hypomania, and euthymia using the *r*-Method-II. Values are expressed as $Median \pm MAD$.

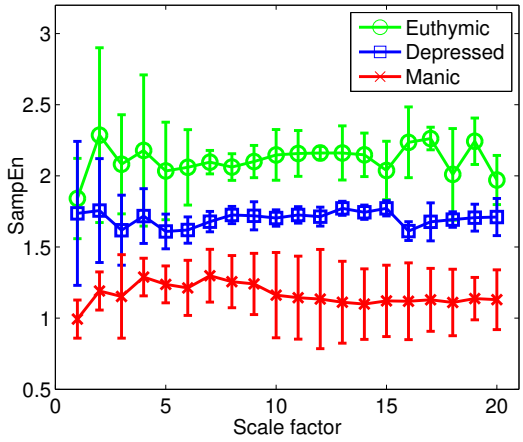

Fig. 3. MSE of heart rate dynamics in nocturnal period with *r*-method-II. Values are expressed as $Median \pm MAD$.

IV. Conclusion and Discussion

In conclusion, we have presented a study on the complexity and multiscale behavior of heartbeat dynamics in bipolar patients through MSE and mQSE analysis of long term RR series. The choice of multiscale 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 [8]. In particular, significant lower complexity has been found in patients with depression as compared to healthy subjects.

We considered both the standard $r - Method - I$ (with r defined as 20% of the signal standard deviation) and a modified $r - Method - II$, which searches for the maximum $ApEn$ values in a parabola interpolating values $0.01 \leq r \leq 1.2$ [24]–[27]. We applied the methods to three pathological mental states: depression, hypomania, and euthymia associated to BD. We found that significantly higher complexity at all scales is associated to the euthymic state (the mental state of good affective balance), that the depression state shows significantly lower complexity when compared to the euthymic state, and that hypomanic states show lowest complexity values ($p < 0.01$) than both other two states. Of note, the differences in complexity found among the three pathological mood states are not biased by the age of the patients enrolled in the study. As a matter of fact, 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.

Our results confirm a significant decrease of complexity patterns in pathological mood states [7], [8], [13], opening to the possibility for extending the current knowledge on objective psycho-physiological markers. Moreover, it is well-known in the current literature that cardiovascular dynamics are strongly affected by central processing [8], [13], [14], [31].

Our results advocate the use of a more objective method for the *SampEn* estimation over the scale factors, which involves a proper choice of the r value, which is more appropriate when dealing with long term recordings on patients with different mental states [24], [25], [27]. Because 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, even when verbal reviews are not possible. BD, in fact, is a chronic severe disease [32] which strongly affects the patients' quality of life, even during euthymic states [33], and to date there are no objective biological/physiological markers currently available to monitoring the response to treatment.

This study has been performed within the frame of the PSYCHE project [13], [14], [28], where a multidisciplinary and multi-parametric analysis of BD through the processing of several behavioral, biochemical, and electrophysiological variables has been carried out. Future work will focus on the estimation of a simple index representing the complexity modulation among the three mood states and all scale factors as well as extending the MSE analysis to long term acquisitions during the day, involving also healthy subjects.

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