Predicting Mood Changes in Bipolar Disorder through Heartbeat Nonlinear Dynamics

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***Abstract*—Bipolar Disorder (BD) is characterized by an alternation of mood states from depression to (hypo)mania. Mixed states, i.e., a combination of depression and mania symptoms at the same time, can also be present. The diagnosis of this disorder in the current clinical practice is based only on subjective interviews and questionnaires, while no reliable objective psychophysiological markers are available. Furthermore, there are no biological markers predicting BD outcomes, or providing information about the future clinical course of the phenomenon. To overcome this limitation, here we propose a methodology predicting mood changes in BD using heartbeat nonlinear dynamics exclusively, derived from the ECG. Mood changes are here intended as transitioning between two mental states: euthymic state (EUT), i.e., the good affective balance, and non-euthymic (non-EUT) states. Heart Rate Variability (HRV) series from 14 bipolar spectrum patients (age: 33.43±9.76, age range: 23-54; 6 females) involved in the European project PSYCHE, undergoing whole night ECG monitoring were analyzed. Data were gathered from a wearable system comprised of a comfortable t-shirt with integrated fabric electrodes and sensors able to acquire ECGs. Each patient was monitored twice a week, for 14 weeks, being able to perform normal (unstructured) activities. From each acquisition, the longest artifact-free segment of heartbeat dynamics was selected for further analyses. Sub-segments of 5 minutes of this segment were used to estimate trends of HRV linear and nonlinear dynamics. Considering data from a current observation at day t_0, and past observations at days (t_{-1}, t_{-2},...,), personalized prediction accuracies in forecasting a mood state (EUT/non-EUT) at day t_{+1} were 69% on average, reaching values as high as 83.3%. This approach opens to the possibility of predicting mood states in bipolar patients through heartbeat nonlinear dynamics exclusively.**

***Index Terms*—Mood Recognition, Wearable Systems, Autonomic Nervous System, Heart Rate Variability (HRV), Bipolar Disorder, Pervasive Monitoring.**

I. Introduction

Bipolar Disorder (BD) is a chronic mental illness characterized by alternating phases of depression and phases so-called manic or hypomanic. During depressive states, patients experience symptoms ranging from sadness, hopelessness (including suicidal ideation), loss of energy, anhedonia, and psychomotor retardation [1], [2]. When patients are in manic or hypomanic states, they show symptoms related to pathological hyperactivity, characterized by euphoria or irritability, excessive energy, hyperactivity, hypertrophic self-esteem, reduction in the need of sleep, and psychomotor acceleration [1], [2]. Mixed states, i.e., a combination of depressive and maniac symptoms, can also be present [1], [2]. In the intervals between these pathological episodes, patients typically experience periods of relatively good affective balance, which are called euthymia (EUT). The duration of each mood state and the interval between them are extremely variable from patient to patient, and can occur in different moments of life. Although these mood episodes typically last for weeks, there are conditions in which they happen more frequently. As a matter of fact, in cyclothymia, fluctuations can be on a daily base, being the cause of significant distress or impairment in social, occupational, or other important areas of functioning [3]. Cyclothymic fluctuations are related to the bipolar mood disorder spectrum, and usually occur in short intervals (days/months).

Bipolar disorder is very common in western population [4]–[7]. A recent worldwide survey in 11 countries has found an overall lifetime prevalence of 1% for the typical forms of bipolar disorder and 1.4% for milder subthreshold disorders [2]. BD is also a leading cause of premature mortality due to suicide and associated medical conditions, such as diabetes mellitus and cardiovascular disease [8]. Despite the fact that the recurrent nature of manic and depressive episodes often leads to high direct and indirect health care costs, the clinical assessment and management of this condition is based only on clinician-administered rating scales, clinical interviews and/or subjective evaluations exclusively [9]. Although these interviews are 'structured' (i.e. questions and question order are established and defined in specific manuals) and high rates of consensus can be achieved among specialists (psychiatrists and clinical psychologists), the diagnosis is always based on subjective clinician observation, on the patient's subjective description, and on the physician's interpretation of such description. The most important diagnostic system is based on the criteria proposed by the Diagnostic Statistic Manual of Mental Disorders (DSM) edited by the American Psychiatric Association. The 5th edition of the DSM has been recently released [3]. According to this classification, the diagnosis of depressive episodes is made if the patient exhibits 5 out of 9 possible symptoms. Similar cut-offs are applied for the diagnosis of the other types of mood episode. In line with this approach, a patient who has had only 4 symptoms of depressive episodes is considered remitted (although partially

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remitted). These clearly can bring to biased interpretation and inconsistency [10]–[12].

While it is well known that several neurological disorders such as epilepsy [**?**], [**?**] or parkinsonisms [**?**], [**?**] are associated with Autonomic Nervous System (ANS) dysfunction, this type of association has also been taken into account to objectify the diagnosis of BD [13]–[16]. Specifically, features of hormonal, immunologic, and ANS dysregulation [13], [14] were significantly associated to BD, also estimated by analyzing Heart Rate Variability (HRV) series [15], [16]. Specifically, Latalova et al. [15] found negative correlations between level of dissociation measured by DES (Dissociative Experience Scale) and most of parameters of ANS, and also found negative correlations between the age of the patient and activity of ANS, and between activity of ANS and duration and onset of disorder, whereas Cohen et al. [16] found that euthymic bipolar patients at rest are characterized by lower HRV than healthy controls, independently from specific drug treatments.

As a matter of fact, mood disorders have been previously associated with alterations in ANS functioning [17], [18]. Depressed subjects frequently present clinical symptoms related to autonomic dysfunction such as sleep pattern alterations, decreased appetite, gastrointestinal paresthesia and increased sweating [19]. In addition, multiple studies have reported decreased HRV and baroreflex sensitivity in these subjects [20]. However, none of these studies have reached an acceptable level of accuracy for clinical use in order to forecast the clinical course in single patients. A possible explanation for these negative results can be that mood disorders are very heterogeneous, in terms of psychophysiological, neuroendocrine and neurobiological correlates, with respect to relatively simple clinical phenotypes usually adopted for clinical and also for research purposes. This can also be reflected by different alterations of the ANS dynamics which may affect HRV in different ways. As a consequence, if only one or few HRV metrics are considered, as performed in previous studies, such dishomogeneity cannot be caught. This might result in gathering subjects in groups that, although homogeneous in a clinical descriptive point of view, are extremely dishomogeneous in terms of endophenotypes. Another possible explanation may be found in the type of analysis used. All the studies have used a group analysis approach being able to find significant differences between bipolar patients and healthy controls. However, for clinical purposes, analysis should be performed on a subject-specific basis.

In a recent study [21], we presented a multi-parametric approach that was successfully applied as a decision support system for the clinical assessment of BD. We demonstrated that a single-variable approach, as proposed by the previous literature, is not sufficient to robustly characterize mood episodes [21]. Furthermore, we found remarkable information in the temporal dynamics of a patient's mood episodes [22]. In the current clinical practice, in fact, no temporal and chronological information about the fluctuations of mood are taken into account. Conversely, we found that a given pathological mental state of BD strictly depends on the previous mood state [22]. From a signal processing point of view, patients' mood changes are modeled as a discrete-time stochastic process in which each recording, associated to a specific mood state, also depends on the previous state in agreement with the so-called Markov property [22]. Of note, a congruent temporal trend in nonlinear cardiovascular measures were found when passing from severe states of BD to remission [23]. In other words, it was found that the "current" mood state in BD is dependent on the previous mood state, and it is likely to contain information related to the subsequent state as well.

Although these approaches can be effective in supporting clinical assessment and decision related to BD, none of them have demonstrated any prediction capability among mood states. The early knowledge of ANS signs able to predict the onset of pathological states from euthymia can be an effective tool of BD prevention against potential self-destructive acts or excessive aggression towards others. To this extent, in this study, we propose a methodology predicting mood changes using heartbeat linear and nonlinear dynamics. Such changes are intended as transitioning between euthymic state (EUT), i.e., the good affective balance, and non-euthymic state (non-EUT) - which means fulfilled the criteria for one of the mood states defined above -, and vice-versa.

Likewise the mentioned previous studies [21]–[23], data used in this work were gathered in the framework of the European project PSYCHE (Personalised monitoring SYstems for Care in mental HEalth), which aimed to longitudinally study BD patients through comfortable wearable systems [21]–[27]. A brief overview of the PSYCHE system and the experimental protocol, along with details on the methodology of signal processing for mood prediction, and experimental results follow below.

II. Materials and Methods

A. The PSYCHE System

PSYCHE stands for Personalized monitoring SYstems for Care in mental HEalth and identifies a personalized, pervasive, cost-effective, and multi-parametric system for the long-term and short-term acquisition of data gathered from patients affected by mood disorders [21]. The PSYCHE system supports a novel approach for bipolar disease management based on the paradigm that quasi-continuous monitoring in a natural environment is able to provide parameters, indices and trends for assessing the mood status as well as supporting patients, predicting and anticipating treatment response in its early phase, preventing relapse and alerting physicians in case of a critical event. The system also includes a centralized server performing data-mining procedures for mood evaluations, along with a user-friendly patient interface (e.g., on a smartphone), and a professional web-based interface used by clinicians to administer evaluation questionnaires, look at physiological variable variations, communicate with patients, etc. (see the PSYCHE concept of decision support system for bipolar disorder on Fig. 1). Several signals can be taken into account for the patient's physiological monitoring such as voice [28], activity index, sleep pattern alteration [29], electrodermal response [30], respiration activity, and electrocardiogram (ECG) [21].

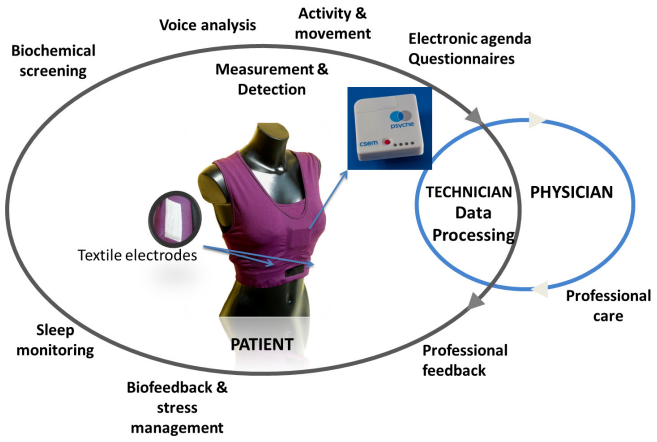

Fig. 1. Overview of the PSYCHE system as global platform serving as decision support system for bipolar disorder management.

In this study, we used the core sensing system of the project, i.e. the PSYCHE wearable monitoring platform [21], developed by Smartex s.r.l (Pisa, Italy) and consisting of a comfortable sensorized t-shirt having dry textile-based electrodes that acquire the patient's ECG, a piezoresistive sensor to acquire the respiration signal, and a three axial accelerometer to track movement. The use of dry textile-based electrodes makes the system easy to use, and allows to maximize comfort and to locate the sensors automatically. The sensorized t-shirt was designed following both a female and male model and is made of elastic fibers that allow for tight adhesion to the user's body. In this work, a comfortable t-shirt having two textile ECG electrodes integrated in the inner side of the front part, below the pectoral muscles in men and the breasts in women was used. The two ECG electrodes are finally connected to the portable electronics, which is connected to the garment through a simple plug that can be easily unplugged when necessary.

We used ECG-derived HRV series coming from the PSYCHE wearable monitoring platform in order to extract the inter-beat interval series (HRV series), i.e. the series constituted by the distance of two consecutive peaks of the ECG in a patient as a non-invasive biomarker of ANS dynamics [31]. Data acquisition is fully implemented in the embodied electronic device of the PSYCHE wearable monitoring platform and includes also part of the pre-processing step. Specifically, the analog ECG is acquired and conditioned by means of an instrumentation amplifier and filters. Then, the ECG is digitalized with a sampling frequency of 250 Hz and stored into the microSD card for further analysis.

B. Experimental Setup and Data Acquisition

This study was designed to test the ability of the proposed methodology, using the PSYCHE system, to predict mood changes in cyclothymic and rapid-cycling bipolar disorders subjects. Specifically, we enrolled 14 patients (age: 33.43±9.76, age range:23-54; 6 females) including 6 rapid-cycling bipolar patients, 4 patients with cyclothymic disorders, and 4 subjects with cyclothymic temperament. At inclusion, 8 subjects were not prescribed any psychotropic medication. None of the subjects was known to suffer from cardiac arrhythmia or significant cardiovascular disease needing drug treatment. The following psychotropic medications were prescribed at inclusion: Antidepressants (fluoxetine): 1 subject (P1); mood stabilizers (lamotrigine 4; lithium 2; pregabaline 1): 5 subjects (P5, P6, P10, P12, P14); antipsychotics (quetiapine 4; aripiprazole 2; cyamemazine 1): 5 subjects (P5, P6, P11, P12, P14); benzodiazepine-like: 2 subjects (P5 and P11). See patients details in the online Supplementary Material. Mood states were defined during the clinical interview according to the scores from two different rating scales: Quick Inventory of Depressive Symptomatology Clinician Rating (QIDS-C16) and Young Mania Rating Scale (YMRS). More specifically, depression was diagnosed when QIDS-C16 score was greater than or equal to 8, hypomania when YMRS score was greater than or equal to 6, and mixed state when QIDS-C16 score was greater than or equal to 8 and YMRS score was greater than or equal to 6. The cut-off for the QIDS-C16 was set at 8 as it is considered equivalent to an HDRS-17 (Hamilton Depression Rating Scale 17 items) score of 10. Such a score on the HDRS has been proposed as a threshold to define recurrence or relapse [**?**]. For the YMRS, the score of 6 for hypomania is quite a standard threshold to quantify the lack of hypomanic symptoms. Such a value is in between the strict threshold definition at 4 [**?**], and the less stringent definition at 8 [**?**]. Euthymic state, i.e., clinical remission, was defined by having a score below the thresholds above mentioned for both the scales.

The study took place in the psychiatry department of the University Hospital of Strasbourg and Geneva.

Inclusion/exclusion criteria adopted for patients recruitment can be found in [21], [22]. Briefly, patient recruitment was performed according to the following criteria:

- Age between 18-65
- 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, cardiovascular-related diseases)
- Absence of cognitive impairment
- Absence of substance abuse disorders
- Willingness of all patients to sign the informed consent for the PSYCHE project approved by the ethical committee of the University of Strasbourg and Geneva.

Individuals with cyclothymia and cyclothymic temperament, or with rapid cycling bipolar disorder were recruited in the general population via ads in newspapers and universities and in clinical populations (patients followed by the clinical investigators). Participants were interviewed at first by phone. During this preliminary phone interview they were asked to fill out the 12-item cyclothymic subscale from the short version of the Temperamental Evaluation of Memphis, Pisa, Paris and San Diego or TEMPS-A. If the screening outcome was positive the patients were recruited. Cyclothymia had to be confirmed

by a clinical assessment based on the DSM-IV-TR criteria of cylothymic disorder and the Akiskal criteria of cyclothymia.

Participants were asked to wear the sensorized shirt during the evening and night twice a week for 14 weeks. They were free to perform daily activities at home or elsewhere while the aforementioned physiological signals were monitored and stored in a microSD card. Participants used the system during the night from 8 p.m. until morning, after wake-up time, until the time the subject takes a shower and/or wants to get dressed. Then, patients were asked to take the system back to their physician, and the recorded data was manually sent to a central database. Accordingly, each patient can be represented by a series of consecutive mood states.

C. Methodology of Signal Processing

The ECG signal was pre-filtered through a tenth order band-pass finite impulse response filter with cut-off frequencies of 0.05-35 Hz approximated by the Butterworth polynomial. Considering that the patients wearing the sensorized shirt could move during the acquisition, and that textile electrodes could lose contact with the skin during body movement, an ad-hoc algorithm for the automatic removal of movement artifacts was applied [21]. To this aim, the maximum and minimum envelopes of the ECG filtered in the bandwidth from 0.1 Hz to 4 Hz were calculated. Afterwards, movement artifacts were detected by using simple statistical thresholds, i.e. 95^{th} percentile, on the average envelope above which the signal is considered affected by artifacts. This automatic artifact detection procedure was applied together with a visual inspection check in order to confirm the actual presence of artifacts in the automatically identified parts of signal, as well as to identify missed parts of the signal actually including artifacts.

In the RR series extraction, referring to the change of the beat interval corresponding to the R-peak, the well-known automatic algorithm developed by Pan-Tompkins [32] was adopted for automatic R-wave detection. Checking for eventual ectopic beats was made in all of the recordings through a previously proposed automatic algorithm based on point-process models [**?**].

A general block scheme of the signal processing chain for mood prediction is shown in Figure 2. From each acquisition the longest artifact-free segment of signal was selected through the previously developed methodology for artifact detection and removal described above [21], including visual inspection. Sub-segments of 5 minutes of this segment were used to calculate informative features, which were defined in the time and frequency domains, as well as from nonlinear analysis (see [31] for calculation details and related literature review). Further analyses such as R peaks and feature extraction were performed in all of the available artifact-free, non-overlapped time windows of 5 minutes. Parts of the signals with artifacts together with consecutive artifact-free ECG signals having dynamics less than five minutes were discarded and not considered for further analysis. The window length of 5 minutes was chosen in order to fulfill the stationarity requirements in analyzing long-term RR series (see recommendations in [31]).

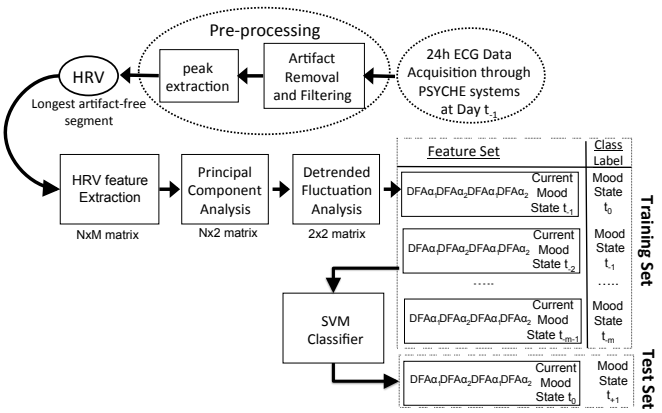

Fig. 2. Block scheme of the proposed signal processing chain for mood prediction between EUT/non-EUT class.

TABLE I
LIST OF HRV FEATURES USED TO ESTIMATE LINEAR AND NONLINEAR ANS DYNAMICS IN PATIENTS BD, WITHIN A LONG-TERM ACQUISITION.

Time domain	Frequency domain	Nonlinear Analysis
Mean RR	VLF peak	Poincaré SD1
Std RR	LF peak	Poincaré SD2
RMSSD	HF peak	Approximate Entropy (ApEn)
pNN50	VLF power	Sample Entropy (SampEn)
RR triangular index	VLF power %	DFA $\alpha 1$
	LF power	DFA $\alpha 2$
	LF power %	RPA Shannon Entropy
	LF power n.u.	RPA Lmin
	HF power	RPA Lmax
	HF power %	RPA Lmean
	HF power n.u.	RPA LAM
	LF/HF power	RPA REC
		RPA DET

Concerning feature extraction, briefly, given the RR interval series, the analysis is performed by extracting informative features using the state of the art for assessing the autonomic regulation of the heart rate [31]. In particular, standard parameters that are defined in the time and frequency domain and are correlated to the sympatho-vagal balance as well as nonlinear measures are taken into account. A detailed list of these parameters is reported in Table I.

Time domain features include the average and standard deviation of the RR intervals (Mean RR and Std RR, respectively), the square root of the mean of the sum of the squares of differences between subsequent RR intervals (RMSSD), and the number of successive differences of intervals which differ by more than 50 ms (expressed as a percentage of the total number of heartbeats analyzed, pNN50). Moreover, the triangular index was calculated as a triangular interpolation of the HRV histogram. All extracted features in the frequency domain were based on the Power Spectral Density (PSD) of the HRV. An auto-regressive (AR) model was used to estimate the PSD in order to provide better frequency resolution than in non-parametric methods. The model order p was estimated according to the Akaike information criterion. The Burg method was used to obtain the AR model parameters. The

standard frequency domain parameters were: VLF (very low frequency), this spectral component in general below 0.04 Hz; LF (low frequency), ranging between 0.04 and 0.15 Hz, and HF (high frequency), which is up to 0.4 Hz. For each of the three frequency bands, along with the band power, the peak value corresponding to the frequency having maximum magnitude was also evaluated. Moreover, the LF/HF ratio was calculated in order to quantify sympathovagal balance and to reflect sympathetic modulations [31].

Several nonlinear HRV measures were also extracted along with the standard morphological and spectral features [31]. Even if the physiological meaning of these features is still unclear, they resulted to be an important quantifier of cardiovascular control dynamics mediated by the ANS [**?**], [**?**], [**?**], [**?**], [31], [33]–[35]. Nonlinear measures are referred to as features extracted by means of the phase space (or state space). Once the phase space is estimated (by means of the so-called embedding procedure), the parameters that appear related to an ANS modulation were evaluated. More specifically, sample entropy and approximate entropy (ApEn and SampEn, respectively) [31], features from the recurrence plot [31] by means of the recurrence quantification analysis (RQA) [31], and the detrended fluctuation analysis (DFA) [31] were evaluated. The calculation of the two entropy measures, ApEn and SampEn, was performed considering the embedding dimension $m = 2$ and the radius $r = 0.2StdRR$, as proposed in [36]. The DFA method quantifies short-term and long-term correlations in the series through the α_1 and α_2 features. While $\alpha 1$ represents the fluctuation in range of 4-16 samples, $\alpha 2$ refers to the range of 16-64 samples [37]. RQA was chosen to quantify the number and the duration of recurrences of the considered cardiovascular dynamical system. The following features were calculated [31]: recurrence rate (RPA REC), determinism (RPA DET), laminarity (RPA LAM), average diagonal line length (RPA Lmean), entropy (RPA Shannon Entropy), and shortest and longest diagonal line (RPA Lmin and RPA Lmax, respectively).

To this extent, for each acquisition of each patient, we obtained a representative NxM matrix (N: number of windows x M: number of features), describing the evolution over time of the feature space. Principal component analysis was then applied on this matrix, and the first two dimensions were retained for further analyses. This choice was justified by the fact that, in most cases, such first two dimensions explained more than 90% of data variance. The time evolution of each these dimensions was synthesized through DFA, taking the α_1 and α_2 parameters as estimates for the short- and long-term correlation, respectively. Along with the features coming from DFA analysis, current mood state was also included as an input feature. This choice is motivated by the fact that, in a previous study [22], we demonstrated that mood changes in bipolar patients can be represented as a stochastic process with Markovian properties. In other words, considering data from a current observation at day t_0, and past observations at days (t_{-1}, t_{-2},...,), we aim to perform a personalized prediction of a mood state between EUT/non-EUT at day t_{+1}. A graphical representation of this concept is shown in Figure 3.

Finally, the actual prediction of the future mood state relied

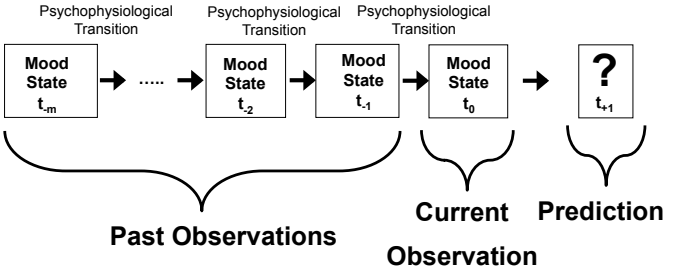

Fig. 3. Graphical representation of mood state temporal dynamics of a given patient with BD.

on Support Vector Machine (SVM) algorithms. Specifically, we adopted common nu-SVM (nu $= 0.5$) having a radial basis kernel function with $\gamma = n^{-1}$, with n=5 equal to the diminution of the feature space.

For each participant, we trained the SVM using a sufficient number of the first few collected samples (for details see Table III), and the remaining samples were used to test its performance. Specifically, the training set included at least one example of EUT, and non-EUT state. All of the algorithms were implemented by using $Matlab$© v7.3 endowed with an additional toolbox for statistical mapping, i.e., LIBSVM [38].

III. Experimental Results

In this study, results were achieved considering data gathered from 14 patients. As mentioned in the previous section, from each acquisition of each patient, the longest artifact-free segment of signal was selected. Table II reports average lengths, across all observations of each patients, of acquired signals and longest artifact-free segments.

TABLE II
AVERAGE LENGTHS OF ACQUIRED AND LONGEST ARTIFACT-FREE SIGNALS AN EXPRESSED IN SECONDS

Patient ID	Acquired signal	Longest Artifact-free segment
P1	26120.37 ± 7149.69	22350 ± 11400
P2	5889.30 ± 5990.24	5700 ± 6000
P3	22743.92 ± 19339.44	11400 ± 4800
P4	10990.78 ± 15108.46	10800 ± 5625
P5	9007.48 ± 4661.27	6150 ± 2400
P6	25492.20 ± 6865.27	16950 ± 14700
P7	28077.65 ± 4320.94	27600 ± 3900
P8	6957.64 ± 7864.32	5400 ± 3975
P9	25924.71 ± 12516.53	17400 ± 6600
P10	29916.71 ± 9192.53	22800 ± 11925
P11	30468.44 ± 5604.22	25200 ± 9675
P12	31165.16 ± 3654.47	12600 ± 3300
P13	20242.29 ± 5790.03	10500 ± 2250
P14	30400.33 ± 9032.32	14700 ± 4575

Ranges are expressed in seconds as $median \pm interquartile - range$

During the acquisitions in Strasbourg, P_3 interrupted the study for 5 weeks between acquisition number 21 and number 22 due to summer holidays. For three other patients, P_1, P_5 and P_8, study duration has to be shortened respectively to 13, 12 and 11.5 weeks due to different factors (P_1: leaving for summer holidays; P_5: delay in study inclusion due to personal unavailability; P_8: delay in enrolling the patient due to the prolongation of the participation of P_3 in the study).

Personalized prediction accuracies in forecasting the mood state (EUT/non-EUT) at time t_{+1} are shown in Table III. In this table, the second column reports the total number of acquisitions used for the accuracy estimation, whereas the third column reports the number of acquisitions used for the initial training set ($x : y$ means that the initial training set was considered from acquisition x to acquisition y).

TABLE III
EXPERIMENTAL RESULTS EXPRESSED AS PREDICTION ACCURACY FOR EACH PATIENT. THE TOTAL NUMBER OF AVAILABLE ACQUISITIONS ('N. ACQ.', SECOND COLUMN), AND THE NUMBER OF ACQUISITIONS TAKEN AS INITIAL TRAINING SET ('TRAINING ACQ.', THIRD COLUMN) ARE ALSO REPORTED.

Patient ID	N. Acq.	Training Acq.	Prediction Acc.
P_1	22	1:5	70.6%
P_2	18	1:3	75%
P_3	14	1:3	60%
P_4	15	1:3	83.3%
P_5	8	1:3	60%
P_6	19	1:4	73.33%
P_7	22	1:4	77.78%
P_8	10	1:2	42.85%
P_9	18	1:5	70%
P_{10}	12	1:3	80%
P_{11}	18	1:3	66.67%
P_{12}	8	1:3	66.67%
P_{13}	16	1:9	71.43%
P_{14}	8	1:3	66.67%

Fig. 4 shows exemplary feature trends from one representative patient among non-euthymic (N) and euthymic (E) mood states.

In addition to accuracy, reported in Table III, the classifier performance was evaluated also in terms of sensitivity, specificity, positive predictive value and negative predictive value. Results are reported in Table 3.

TABLE IV
EXPERIMENTAL RESULTS EXPRESSED AS PERCENTAGE AMONG PATIENTS.

Accuracy	69%
Sensitivity	57%
Specificity	78%
Positive Predictive Value	60%
Negative Predictive Value	76%

Importantly, prediction accuracies reported in Table III should be considered as a snapshot of all possible prediction accuracies related to a given patient. As an example, we report in Figure 5 trends of the prediction accuracy as a function of different observations, considering data gathered from 4 patients. It is possible to recognize trends in which higher accuracy is associated with the first predictions and, then, the accuracy decreases, as well as trends in which the lower recognition accuracy is associated with first the predictions.

In order to investigate which feature could provide a major contribution in forecasting the next mood state, a further analysis based on the circle of correlation of the PCA transformation matrix was performed. Table IV shows the first 5 mostly correlated features for each patient. An exemplary plot from one subject of such analyses is reported below in Fig. 6.

This analysis was performed considering the PCA calculation on all the acquisitions of each patient, and suggests that

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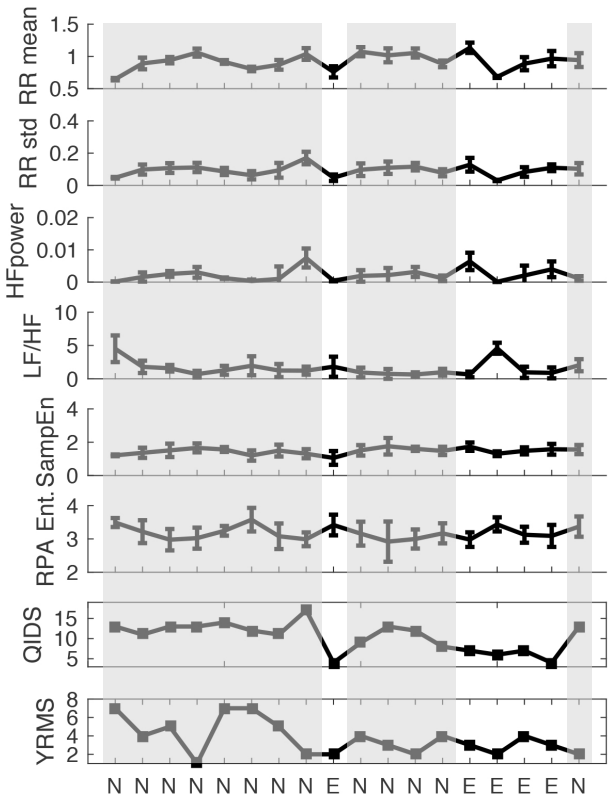

Fig. 4. Exemplary feature trends from one patient among non-euthymic (N) and euthymic (E) mood states.

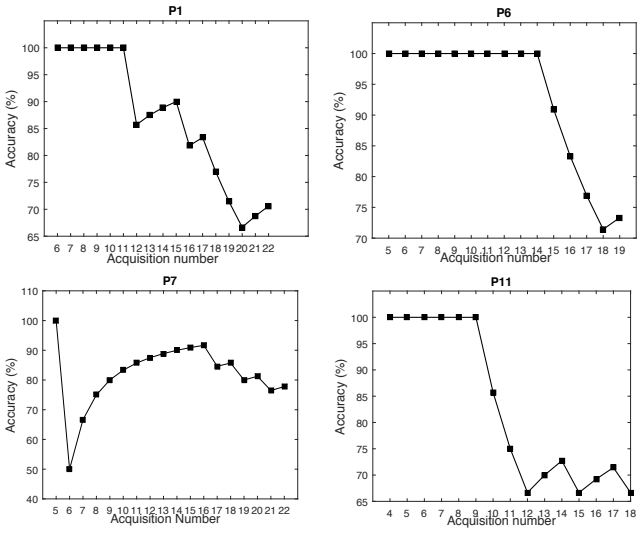

Fig. 5. Exemplary trends of prediction accuracy as a function of the acquisition number in four patients.

the HRV features reported in Table V are the most informative in forecasting the next mood state.

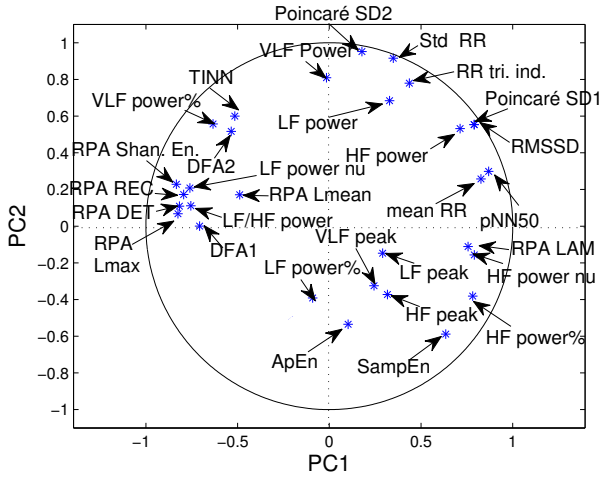

Fig. 6. Circle of Correlation obtained from one exemplary patient (P_2).

TABLE V
FIRST 5 MOSTLY CORRELATED FEATURES AMONG PATIENTS, PREDICTING MOOD CHANGES.

HRV Feature	Frequency
Std RR	12/14
RMSSD	11/14
Poincaré SD1	11/14
Poincaré SD2	11/14
HF power	8/14

IV. DISCUSSION AND CONCLUSION

We reported promising results suggesting that it is possible to forecast mood states in BD and in cyclothymic temperament subjects using heartbeat dynamics exclusively, gathered from ECG. Here, we reduced the problem predicting two possible mental states: the euthymic state, i.e., the good affective balance, and non-euthymic state, i.e., every mood state of BD among depression, hypomania, and mixed state.

Results of this study are very encouraging and promising. At a group-wise level, prediction accuracy was, on average among all patients, of 69%. We are aware that such an average accuracy is not so high but, as a preliminary and pioneering achievement, we consider it as satisfactory and promising. We also consider these results as a preliminary outcome due to the fact that the class non-EUT actually includes three mood states, making therefore the EUT class likely to be underrepresented. This may justify an average sensitivity of the system of 57%, and positive predictive value of 60%. However, it is important to note that at a single patient level we reached prediction accuracy as high as 83.3%, considering also that such a prediction accuracy strongly depends on the number of acquisitions and related mood states (see Figure 5).

Through a circle of correlation analysis, we found that features related to the parasympathetic activity (Std RR, RMSSD, and HF power), as well as HRV nonlinear dynamics (Poincaré SD1 and SD2) are the most significant measures to predict mood changes. This is in agreement with the previous literature pointing out parasympathetic dysfunction in BD [39], [40] (as a counter-proof, vagus nerve stimulation appears to be a promising intervention for the treatment of BD [41]), and a crucial role of ANS nonlinear dynamics [21], [25], [42], [43]. Importantly, these alterations are known to contribute to early cardiovascular disease [44]. Our results can also be read in the light of a current opinion proposing that the complexity of mental illness can be studied under a general framework by quantifying the order and randomness of dynamic macroscopic human behavior and microscopic neuronal activity [43].

Although previous studies suggested possible biomarkers to support the diagnosis of BD [13]–[16], none of these studies have shown predictive capability as well as an acceptable level of accuracy for clinical use. We focused on intra-subject analysis also to allow finding possible personalized correlations between the pattern of physiological signals and mood fluctuations, which are much more interesting for the psychiatric community. The recruitment of cyclothymic subjects offered a good opportunity to test the ability of the PSYCHE system and proposed methodology of signal processing to predict more subtle mood fluctuations and to test prospectively the prediction performance, given the possibility of collecting data about several similar mood sequences in a relatively short time interval.

From a clinical point of view, outcomes of this mood prediction study are very relevant. Knowing in advance whether the patient is getting better or not could effectively help clinicians to optimize the therapy and make changes in time, if necessary. On the other hand, understanding if the patient is going to have a relapse is very important and informative to perform a more accurate clinical monitoring, and plan a treatment at very early stage.

As mentioned above, data of long-term cardiovascular dynamics used in this study were gathered through the PSYCHE platform, developed in the framework of the European project PSYCHE [21]–[26]. The PSYCHE platform consists of a wearable sensorized t-shirt, integrating fabric-based electrodes, able to acquires ECG, respiration signals, and body activity, and a smartphone collecting data from the wearable system via Bluetooth technology. Next developments of this platform will include such capability of predicting the mood. Of note, the platform can also be used to record voice parameters and subjective data (e.g., mood agenda, sleep agenda) as well.

In agreement with the aims of the PSYCHE project, the proposed forecasting methodology is fully personalized, and is based on long monitoring acquisitions regardless of specific activity performed by patients. Each patient observation, in fact, was represented by time-varying HRV linear and nonlinear estimates. Then, further multivariate signal processing synthesized the patient mood state in a 5-dimension feature space. Of note, this approach relies on our previous study [22], which demonstrated that mood changes in bipolar patients can be represented as a stochastic process with Markovian properties, i.e., current mood state depends on the previous one. This is in line also with clinical observations: for instance, a cycle in which mania follows depression and precedes euthymia is associated with a longer depressive status and a lesser intense response to mood stabilizers as compared to a cycle in which depression follows mania and precedes euthymia [45].

We are aware that more acquisitions, possibly with more frequent transitions, can remarkably improve prediction performance and may help to generalize our results to the wider clinical presentation and phenotypes of BD. An ideal mood switch predictor, in fact, would require all possible transitions among mood states, i.e. 16 combinations of mood labels included in the feature space-feature label of the training set: depression-euthymia, depression-depression, depression-mania, depression-mixed state, euthymia-depression, euthymia-euthymia, euthymia-mania, etc. Machine learning systems able to discriminate a so high number of classes are very challenging and require a large volume of data. Such a larger sample would also allow investigating a parameter optimization procedure for SVM classifiers, as well as will focus on a rigorous comparison with other automatic classification methods. Another limitation of this study is a potentially confounding effect of the psychotropic medication in 6 subjects including antidepressants, mood stabilizers, antipsychotics and benzodiazepine-like medication prescribed regularly. Common side effects of psychotropic drugs include anticholinergic and autonomic effects. These effects might have diminished the predictive power of our study. However, in psychiatric practice, patients with mood disorders are very frequently treated with psychotropic medications. Therefore, our results are very encouraging regarding the clinical usability of the PSYCHE system. Additional studies are needed to assess the impact of psychotropic drugs on its predictive power.

In conclusion, we state that the proposed methodology is able to predict the next mood state with acceptable reliability. This system feature is very useful to clinicians because pharmacological treatments are often administered on a trial and error base, i.e., the clinician could know whether a treatment is going to be effective or not looking at clinical course of the patient. Forecasting relapses might reduce negative outcomes in bipolar disorders (e.g., suicide attempts) and provide a more rapid onset of effective treatments. Moreover, predicting whether a patient is getting better could let the hospital facilities to better organize the hospitalizations.

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REFERENCES

[1] A. P. Association *et al.*, "Practice guideline for the treatment of patients with bipolar disorder (revision)." *The American journal of psychiatry*, vol. 159, no. 4 Suppl, p. 1, 2002.

[2] K. R. Merikangas, R. Jin, J.-P. He, R. C. Kessler, S. Lee, N. A. Sampson, M. C. Viana, L. H. Andrade, C. Hu, E. G. Karam *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.

[3] A. P. Association *et al.*, *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. American Psychiatric Pub, 2013.

[4] R. Kessler, K. McGonagle, S. Zhao, C. Nelson, M. Hughes, S. Eshleman *et al.*, "Lifetime and 12-month prevalence of dsm-iii-r psychiatric disorders in the united states: results from the national comorbidity survey," *Archives of general psychiatry*, vol. 51, no. 1, p. 8, 1994.

[5] H. Wittchen and F. Jacobi, "Size and burden of mental disorders in europe–a critical review and appraisal of 27 studies," *European neuropsychopharmacology*, vol. 15, no. 4, pp. 357–376, 2005.

[6] S. Pini, V. de Queiroz, D. Pagnin, L. Pezawas, J. Angst, G. Cassano *et al.*, "Prevalence and burden of bipolar disorders in european countries," *European Neuropsychopharmacology*, vol. 15, no. 4, pp. 425–434, 2005.

[7] Y. Chen and S. Dilsaver, "Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other axis i disorders," *Biological Psychiatry*, vol. 39, no. 10, pp. 896–899, 1996.

[8] K. R. Merikangas, H. S. Akiskal, J. Angst, P. E. Greenberg, R. M. Hirschfeld, M. Petukhova, and R. C. Kessler, "Lifetime and 12-month prevalence of bipolar spectrum disorder in the national comorbidity survey replication," *Archives of general psychiatry*, vol. 64, no. 5, pp. 543–552, 2007.

[9] A. P. Association *et al.*, *Diagnostic and Statistical Manual of Mental Disorders:: DSM-5*. ManMag, 2003.

[10] E. Vieta, M. Reinares, and A. Rosa, "Staging bipolar disorder," *Neurotoxicity research*, vol. 19, no. 2, pp. 279–285, 2011.

[11] A. Andreazza, M. Kauer-Sant'Anna, B. Frey, D. Bond, F. Kapczinski, L. Young, and L. Yatham, "Oxidative stress markers in bipolar disorder: a meta-analysis," *Journal of affective disorders*, vol. 111, no. 2, pp. 135–144, 2008.

[12] M. Phillips and E. Vieta, "Identifying functional neuroimaging biomarkers of bipolar disorder: toward dsm-v," *Schizophrenia bulletin*, vol. 33, no. 4, pp. 893–904, 2007.

[13] V. Taylor and G. MacQueen, "Associations between bipolar disorder and metabolic syndrome: a review," *Journal of Clinical Psychiatry*, vol. 67, no. 7, pp. 1034–1041, 2006.

[14] B. Levy, "Autonomic nervous system arousal and cognitive functioning in bipolar disorder," *Bipolar disorders*, vol. 15, no. 1, pp. 70–79, 2013.

[15] K. Latalova, J. Prasko, T. Diveky, A. Grambal, D. Kamaradova, H. Velartova, J. Salinger, and J. Opavsky, "Autonomic nervous system in euthymic patients with bipolar affective disorder." *Neuro endocrinology letters*, vol. 31, no. 6, pp. 829–836, 2009.

[16] 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.

[17] R. M. Carney, K. E. Freedland, and R. C. Veith, "Depression, the autonomic nervous system, and coronary heart disease," *Psychosomatic medicine*, vol. 67, pp. S29–S33, 2005.

[18] J. M. Gorman and R. P. Sloan, "Heart rate variability in depressive and anxiety disorders," *American heart journal*, vol. 140, no. 4, pp. S77–S83, 2000.

[19] A. Tylee and P. Gandhi, "The importance of somatic symptoms in depression in primary care," *Primary care companion to the Journal of clinical psychiatry*, vol. 7, no. 4, p. 167, 2005.

[20] A. H. Kemp, D. S. Quintana, M. A. Gray, K. L. Felmingham, K. Brown, and J. M. Gatt, "Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis," *Biological psychiatry*, vol. 67, no. 11, pp. 1067–1074, 2010.

[21] 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.

[22] G. Valenza, M. Nardelli, A. Lanata, C. Gentili, G. Bertschy, R. Paradiso, and E. P. Scilingo, "Wearable monitoring for mood recognition in bipolar disorder based on history-dependent long-term heart rate variability analysis," *Biomedical and Health Informatics, IEEE Journal of*, vol. 18, no. 5, pp. 1625–1635, 2014.

[23] A. Lanata, G. Valenza, M. Nardelli, C. Gentili, and E. P. Scilingo, "Complexity index from a personalized wearable monitoring system for assessing remission in mental health," *Biomedical and Health Informatics, IEEE Journal of*, vol. 19, no. 1, pp. 132–139, 2015.

[24] G. Valenza, L. Citi, C. Gentili, A. Lanatá, E. Scilingo, and R. Barbieri, "Point-process nonlinear autonomic assessment of depressive states in bipolar patients." *Methods of information in medicine*, vol. 53, no. 4, 2014.

[25] G. Valenza, M. Nardelli, G. Bertschy, A. Lanata, and E. Scilingo, "Mood states modulate complexity in heartbeat dynamics: A multiscale entropy analysis," *EPL (Europhysics Letters)*, vol. 107, no. 1, p. 18003, 2014.

[26] G. Valenza, L. Citi, C. Gentili, A. Lanata, E. P. Scilingo, and R. Barbieri, "Characterization of depressive states in bipolar patients using wearable textile technology and instantaneous heart rate variability assessment," *Biomedical and Health Informatics, IEEE Journal of*, vol. 19, no. 1, pp. 263–274, 2015.

[27] A. Greco, G. Valenza, A. Lanata, G. Rota, and E. P. Scilingo, "Electrodermal activity in bipolar patients during affective elicitation," *Biomedical and Health Informatics, IEEE Journal of*, vol. 18, no. 6, pp. 1865–1873, 2014.

[28] N. Vanello, A. Guidi, C. Gentili, S. Werner, G. Bertschy, G. Valenza, A. Lanata, and E. P. Scilingo, "Speech analysis for mood state characterization in bipolar patients," in *Engineering in Medicine and Biology Society (EMBC), 2012 Annual International Conference of the IEEE*. IEEE, 2012, pp. 2104–2107.

[29] S. Mariani, M. Migliorini, G. Tacchino, C. Gentili, G. Bertschy, S. Werner, and A. M. Bianchi, "Clinical state assessment in bipolar patients by means of hrv features obtained with a sensorized t-shirt," in *Engineering in Medicine and Biology Society (EMBC), 2012 Annual International Conference of the IEEE*. IEEE, 2012, pp. 2240–2243.

[30] A. Greco, A. Lanata, G. Valenza, G. Rota, N. Vanello, and E. Scilingo, "On the deconvolution analysis of electrodermal activity in bipolar patients," in *Engineering in Medicine and Biology Society (EMBC), 2012 Annual International Conference of the IEEE*. IEEE, 2012, pp. 6691–6694.

[31] U. Rajendra Acharya, K. Paul Joseph, N. Kannathal, C. Lim, and J. Suri, "Heart rate variability: a review," *Medical and Biological Engineering and Computing*, vol. 44, no. 12, pp. 1031–1051, 2006.

[32] J. Pan and W. Tompkins, "A real-time QRS detection algorithm," *IEEE Transactions on Biomedical Engineering*, pp. 230–236, 1985.

[33] 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.

[34] A. Goldberger, C. Peng, and L. Lipsitz, "What is physiologic complexity and how does it change with aging and disease?" *Neurobiology of aging*, vol. 23, no. 1, pp. 23–26, 2002.

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

[36] J. S. Richman and J. R. Moorman, "Physiological time-series analysis using approximate entropy and sample entropy," *American Journal of Physiology-Heart and Circulatory Physiology*, vol. 278, no. 6, pp. H2039–H2049, 2000.

[37] C.-K. Peng, S. Havlin, H. E. Stanley, and A. L. Goldberger, "Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series," *Chaos: An Interdisciplinary Journal of Nonlinear Science*, vol. 5, no. 1, pp. 82–87, 1995.

[38] C.-C. Chang and C.-J. Lin, "Libsvm: A library for support vector machines," *ACM Transactions on Intelligent Systems and Technology (TIST)*, vol. 2, no. 3, p. 27, 2011.

[39] 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.

[40] J.-S. Lee, B. Kim, Y. Hong, and Y. H. Joo, "Heart rate variability in the subsyndromal depressive phase of bipolar disorder," *Psychiatry and clinical neurosciences*, vol. 66, no. 4, pp. 361–366, 2012.

[41] M. S. George, H. A. Sackeim, A. J. Rush, L. B. Marangell, Z. Nahas, M. M. Husain, S. Lisanby, T. Burt, J. Goldman, and J. C. Ballenger, "Vagus nerve stimulation: a new tool for brain research and therapy?" *Biological psychiatry*, vol. 47, no. 4, pp. 287–295, 2000.

[42] 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.

[43] A. C. Yang and S.-J. Tsai, "Is mental illness complex? from behavior to brain," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 45, pp. 253–257, 2013.

[44] B. I. Goldstein, M. R. Carnethon, K. A. Matthews, R. S. McIntyre, G. E. Miller, G. Raghuveer, C. M. Stoney, H. Wasiak, and B. W. McCrindle, "Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease a scientific statement from the american heart association," *Circulation*, vol. 132, no. 10, pp. 965–986, 2015.

[45] A. Koukopoulos, D. Reginaldi, L. Tondo, C. Visioli, and R. Baldessarini, "Course sequences in bipolar disorder: depressions preceding or following manias or hypomanias," *Journal of affective disorders*, vol. 151, no. 1, pp. 105–110, 2013.