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Clinical state assessment in bipolar patients by means of HRV features obtained with a sensorized T-shirt

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***Abstract*—The aim of this study is to identify parameters extracted from the Heart Rate Variability (HRV) signal that correlate to the clinical state in patients affected by bipolar disorder. 25 ECG and activity recordings from 12 patients were obtained by means of a sensorized T-shirt and the clinical state of the subjects was assessed by a psychiatrist. Features in the time and frequency domain were extracted from each signal. HRV features were also used to automatically compute the sleep profile of each subject by means of an Artificial Neural Network, trained on a control group of healthy subjects. From the hypnograms, sleep-specific parameters were computed. All the parameters were compared with those computed on the control group, in order to highlight significant differences in their values during different stages of the pathology. The analysis was performed by grouping the subjects first on the basis of the depression-mania level and then on the basis of the anxiety level.**

I. Introduction

PSYCHOLOGICAL states can have a dramatic impact on the dynamic autonomic control of the heart [1]. In fact, it is known how Central Nervous System pathologies are also reflected on the Autonomic Nervous System, and mood changes can affect the heart rate as well as other peripheral signals.

The project PSYCHE [2, 3] is aimed at the development of innovative methods for monitoring psychiatric disorders and pathologies by means of wearable devices that measure signals of easy access, such as the ECG and the body movements. Sleep disturbances are among the most prominent correlates of mood episodes and inadequate recovery [4]. People affected by stress, depression or anxiety tend to have a poorer sleep quality, resulting in lower sleep efficiency, higher values for REM% [5] and shorter REM latency [6, 7]. Furthermore, sleep represents an ideal condition in which HRV parameters can be monitored and related to the clinical state, in fact, sleepers are less prone to be influenced by external stimuli and signals are normally more clear of artifacts [8].

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II. Materials and Methods

A. Data Set

A group of 5 bipolar patients enrolled at the University of Pisa, Italy, and a group of 7 bipolar patients enrolled at the FORENAP R&D S.A.S.U. center, in Rouffach, France, were involved in this study. The inclusion criteria were age 18-65, diagnosis of Bipolar Disorder (I or II [9]), absence of suicidality, absence of delusions or hallucinations at the moment of recruitment, absence of relevant somatic or neurological conditions. Patients underwent periodic visits at the medical centers, in which their mood was assessed by means of clinician-administered rating scales and questionnaires. During the nights following each clinical assessment, the patients wore a sensorized T-shirt (Smartex [2]) that recorded their ECG, respiration and body activity during the whole night. For what concerns the first dataset, both the depression-mania level and the anxiety level were assessed. For the second dataset, only the depression-mania level was assessed. Four clinical states for the depression-mania were used: euthymic (EU), depressed (DE), mixed state (MI), or hypomanic (HY). The anxiety level was scored as A1 (low anxiety state) or A2 (high anxiety state). The clinical states of the subjects are reported in Table I and Table II.

The average duration of the recordings was approximately 7 hours. However, for four recordings, due to movement artifacts, sweating or misplacement of the sensors, the useful signal portion was too short (less than 5 hours) to allow for a significant computation of sleep parameters. For such recordings, outlined with black boxes in Table I, though a partial hypnogram was automatically computed, the parameters Sleep Efficiency and REM% were not taken into account.

TABLE I
PISA DATA SET: DEPRESSION-MANIA AND ANXIETY LEVEL FOR EACH SUBJECT AND ACQUISITION

Patient	*ACQ1*	*ACQ2*	*ACQ3*	*ACQ4*	*ACQ5*	*ACQ6*
1	**DE-A2**	**DE-A2**	**DE-A2**	**EU-A1**		
2	**MI-A2**	**MI-A1**	**DE-A2**	**DE-A1**	**DE-A1**	**EU-A1**
3	**DE-A1**					
4	**EU-A1**					
5	**MI-A1**					

TABLE II
FORENAP DATA SET: DEPRESSION-MANIA LEVEL FOR EACH SUBJECT AND ACQUISITION

Patient	*ACQ1*	*ACQ2*	*ACQ3*
1	**EU**		
2	**HY**	**EU**	**DE**
3	**HY**	**EU**	
4	**DE**	**EU**	
5	**DE**	**HY**	
6	**DE**		
7	**HY**		

A control group of 102 sleep recordings from healthy subjects belonging to the database of the Department of Bioengineering of Politecnico di Milano was used for the computation of normality ranges for all the features.

B. Feature extraction

Three classes of features were extracted from the HRV signal: linear time-domain features, nonlinear time-domain features, and spectral features.

The linear features in the time domain were:

- **MEANNN** – average value of the NN intervals;
- **SDNN** – standard deviation of the NN intervals;
- **RMSSD** – square root of the mean of the sum of the squares of differences between subsequent NN intervals;

The nonlinear time-domain features were:

- **Sample Entropy (SampEn)** – [10];
- **Lempel-Ziv Complexity (LZC)** – [11];
- **Detrended Fluctuation Analysis (DFA) scaling exponents** – [12];
- **1/f Slope** – Slope of the regression line defining the power-law distribution of the HRV.

Features in the frequency domain were computed by applying a Time-Variant AR Model (TVAM) to the HRV time series with 9 coefficients and a variable forgetting factor (Fortescue) to estimate the beat-per-beat power spectrum, and calculating the normalized **VLF** (very low frequency, 0-0.04 Hz), **LF** (low frequency, 0.04-0.15 Hz) and **HF** (high frequency, 0.15-0.4 Hz) power of the spectrum, together with the sympatho-vagal balance LF/HF. These parameters were then averaged on nonoverlapped 30-s-long windows, and the following features were computed for each recording:

- **LFmax** and **LFmin**, maximum and minimum normalized LF power
- **deltaLF**=LFmax-LFmin
- **HFmax** and **HFmin**, maximum and minimum normalized HF power
- **deltaHF**=HFmax-HFmin
- **LF/HFmax** and **LF/HFmin**, maximum and minimum value of the sympathovagal balance during the night
- **deltaLF/HF**=LF/HFmax-LF/HFmin

Also, sleep parameters had to be extracted from each recording. The sleep profile for each night recording was automatically computed by means of a supervised Artificial Neural Network, which classified each 30-second epoch into wake, REM or NREM stage. The network was trained on linear time-domain HRV features and spectral HRV features (for a total of 13 parameters) extracted from the 102 control recordings. For each training vector, the corresponding sleep stages, visually scored by an expert clinician, were used as training labels. The networks had 13 input neurons, one for each HRV feature, one hidden layer with a number of neurons varying from 2 to 30, and 3 output neurons, one for each sleep stage (wake, NREM, REM). The training mode was backpropagation with Levemberg-Marquardt algorithm.

In order to optimize the performance of the final network, a Leave One Out cross-validation method was employed: the initial set of 102 recordings was split 10 times into a training and a testing set, and each time the optimal number of hidden neurons was picked as that allowing for the best classification performance. The final number of neurons in the hidden layer was chosen as equal to 20.

The activity index, obtained as a binary version of the activity signal, was used in order to identify wake epochs *a posteriori*. Fig. 1 shows an example of an automatically computed sleep profile, together with the HRV and activity signals.

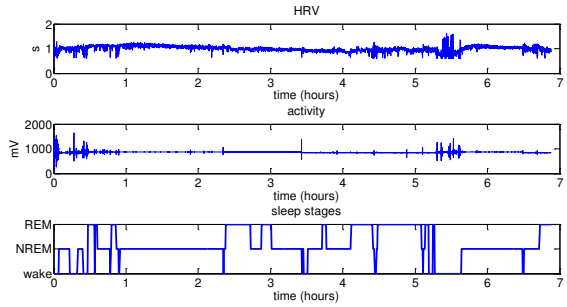

Fig. 1: Automatically computed sleep profile, starting from HRV and activity signals.

C. Statistical tests

After verifying that the groups were not normally distributed, by means of a Kolmogorov-Smirnov test, a Kruskal-Wallis one-way analysis of variance and a multiple comparison t-test after a Bonferroni correction were applied in order to highlight which features could significantly discriminate each class of bipolar patients from the healthy subjects. This was done separately for patients grouped according to the depression-mania level and patients grouped according to the anxiety level.

D. Visual analysis

The parameters, grouped by depression-mania level and by anxiety level, were then plotted with respect to the normality ranges defined on the control subjects (median and first and third quartile of the distribution), in order to highlight their significances in characterizing the clinical state.

III. RESULTS

The mean and standard deviation values for the features computed on bipolar subjects grouped by depression-mania level, compared with the controls, are reported in Table III. Similarly, mean and standard deviation of the features for anxiety (A1 and A2) groups compared with normal subjects

are reported in Table IV. Linear time-domain features are measured in ms, spectral features are measured in normalized units, REM latency is measured in s.

In the rows labelled "classes", the couples of classes between which the values for the features show significant differences, according to the results of the Kruskal-Wallis and the multiple comparison t-test, are reported.

The most significant features are shown in Fig. 2 and Fig. 3. Each red dot on the graphs represents the parameter deriving from a recording, while the blue lines indicate the normality ranges: the solid line represents the median of the distribution, while the dashed lines represent the first and the third quartiles.

IV. Discussion

The graphs reported in Fig. 2 show reduced values of MEANNN in the bipolar patients during mixed-state and hypomanic phases and reduced values of RMSSD, again especially in mixed and hypomanic states.

Differences between the bipolar patients and the group of healthy subjects have been found in the non-linear parameters, such as SampEn values, that are lower for bipolar subjects in mixed and hypomanic state and LZC, which is significantly lower for depressed subjects when compared to healthy subjects.

Regarding the analysis of sleep parameters, it is possible to notice an increased percentage of REM sleep with respect of the total sleep time in all bipolar patients. The Sleep Efficiency is decreased in bipolar subjects in mixed state and hypomanic state. The REM latency is significantly lower for euthymic, depressed and hypomanic bipolar subjects.

The results of the anxiety analysis, according to Fig. 3, show reduced values of MEANNN for both anxiety groups, reduced values of SDNN only for high anxiety patients, reduced values of RMSSD for both groups, but with a stronger significance for high anxiety patients, reduced values of SampEn for both groups and increased values of LZC only for the high anxiety group. The maximum value of the LF power shows higher values in patients with high anxiety. For what concerns sleep parameters, REM% is increased and REM latency is decreased in both anxiety classes.

From the statistical analysis, it can be noticed how some of the computed features – in bold in Table III and Table IV, are significant in discriminating bipolar subjects of several clinical states from healthy subjects. However, both for the depression-mania analysis and for the anxiety analysis, the features alone do not show enough statistical significance in discriminating among different clinical states in pathological subjects. With the final aim of creating a clinical state classifier based on HRV parameters, features should be appropriately combined by means of Data Mining techniques.

It is also important to highlight that such a statistical analysis is only preliminary, since the limited data set employed does not allow for certain results.

TABLE III

Features (mean±standard deviation) for the normal subjects (N), and the euthymic (EU), depressed (DE), mixed-state (MI) and hypomanic (HY) groups.

	MEANNN	SDNN	DFA1	DFA2	1/f	**SampEn**	LZC(2)	**RMSSD**	LF/HF max	LF/HF min
N	1005.7 ±54.56	112.57 ±18.34	0.91 ±0.10	0.91 ±0.06	-1.12 ±0.31	1.38 ±0.24	0.94 ±0.01	86.66 ±13.67	61.63 ±58.37	0.54 ±0.10
EU	795.65 ±136.8	98.93 ±33.47	1.01 ±0.21	0.99 ±0.13	-1.39 ±0.90	0.87 ±0.36	0.98 ±0.01	53.83 ±26.26	116.7 ±149.8	0.67 ±0.23
DE	841.13 ±75.44	89.16 ±45.44	0.92 ±0.15	0.95 ±0.17	-1.39 ±1.10	0.80 ±0.30	0.98 ±0.06	52.47 ±59.65	104.4 ±47.9	0.59 ±0.23
MI	759.84 ±62.75	87.65 ±56.26	0.86 ±0.08	0.70 ±0.18	-0.97 ±0.21	0.78 ±0.52	0.97 ±0.04	86.16 ±69.37	73.36 ±14.56	0.48 ±0.16
HY	796.86 ±87.32	74.22 ±35.95	0.94 ±0.14	1.04 ±0.07	-1.02 ±0.14	0.67 ±0.16	0.99 ±0.01	37.73 ±10.58	301.07 ±143.8	0.38 ±0.05
classes	EUvsN, DEvsN MIvsN HYvsN					EUvsN DEvsN HYvsN	DEvsN	DEvsN HYvsN		

	HFn max	HFn min	LFn max	LFn min	LF/HF delta	HFn delta	LFn delta	**REM Latency**	**Sleep Efficiency(%)**	**REM%**
N	0.67 ±0.12	0.08 ±0.05	0.92 ±0.05	0.33 ±0.12	0.56 ±0.12	0.60 ±0.11	0.60 ±0.11	7473.2 ±5096	84.09 ±14.42	18.29 ±7.30
EU	0.62 ±0.08	0.05 ±0.03	0.95 ±0.03	0.38 ±0.08	0.52 ±0.09	0.57 ±0.06	0.57 ±0.06	1,087 ±985.2	79.03 ±14.26	37.62 ±22.93
DE	0.65 ±0.04	0.04 ±0.03	0.96 ±0.03	0.35 ±0.09	0.54 ±0.10	0.61 ±0.08	0.61 ±0.08	2,251 ±1,512	73.96 ±17.14	45.43 ±32.79
MI	0.70 ±0.04	0.05 ±0.01	0.95 ±0.06	0.30 ±0.04	0.64 ±0.07	0.65 ±0.08	0.65 ±0.08	4,190 ±3,652	80.87 ±17.14	30.19 ±12.79
HY	0.75 ±0.03	0.04 ±0.03	0.96 ±0.03	0.25 ±0.03	0.66 ±0.04	0.71 ±0.04	0.71 ±0.04	85.75 ±67.81	60.57 ±23.47	44.33 ±15.73
classes								EUvsN DEvsN HYvsN	HYvsN	EUvsN DEvsN HYvsN

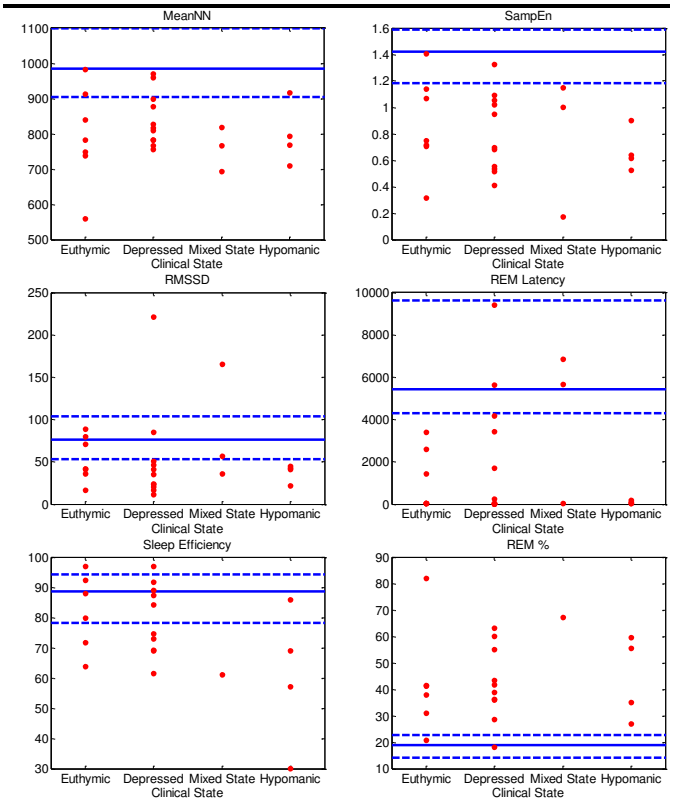

Fig. 2: Values of the most significant features grouped according to the depression-mania level, compared with normality ranges.

TABLE IV

FEATURES (MEAN±STANDARD DEVIATION) FOR THE NORMAL SUBJECTS (N), THE LOW ANXIETY GROUP (A1) AND THE HIGH ANXIETY GROUP (A2).

	MEAN NN	**SDNN**	DFA1	DFA2	1/f	**Samp En**	**LZC(2)**	**RMSSD**	LF/HF max	LF/HF min
N	1005.7 ±54.56	112.57 ±18.34	0.91 ±0.10	0.91 ±0.06	-1.12 ±0.31	1.38 ±0.24	0.94 ±0.01	86.66 ±13.67	61.63 ±58.37	0.54 ±0.10
A1	773.06 ±140.0	97.30 ±36.13	0.96 ±0.13	0.87 ±0.16	-1.03 ±1.00	0.79 ±0.32	0.96 ±0.12	80.41 ±55.03	137.27 ±317.2	0.68 ±030
A2	816.92 ±120.9	69.03 ±55.83	0.90 ±0.23	0.92 ±0.27	-0.84 ±0.35	0.71 ±0.38	0.99 ±0.07	30.32 ±75.04	57.93 ±140.2	0.52 ±0.30
classes	A1vsN, A2vsN	A2vsN				A2vsN A2vsN	A2vsN	A1vsN A2vsN		

	HFn max	HFn min	**LFn max**	LFn min	LF/HF delta	HFn delta	LFn delta	**REM Latency**	Sleep Efficiency(%)	**REM%**
N	0.67 ±0.12	0.08 ±0.05	0.92 ±0.05	0.33 ±0.12	0.56 ±0.12	0.60 ±0.11	0.60 ±0.11	7473.2 ±5096	84.09 ±14.42	18.29 ±7.30
A1	0.62 ±0.11	0.05 ±0.05	0.95 ±0.05	0.38 ±0.11	0.53 ±0.13	0.57 ±0.09	0.57 ±0.09	2330.0 ±3568	72.23 ±27.02	51.73 ±26.93
A2	0.68 ±0.03	0.04 ±0.04	0.96 ±0.04	0.32 ±0.03	0.59 ±0.04	0.63 ±0.04	0.63 ±0.04	4074.0 ±2518	79.87 ±12.43	31.70 ±21.00
classes			A2vsN					A1vsN A2vsN		A1vsN A2vsN

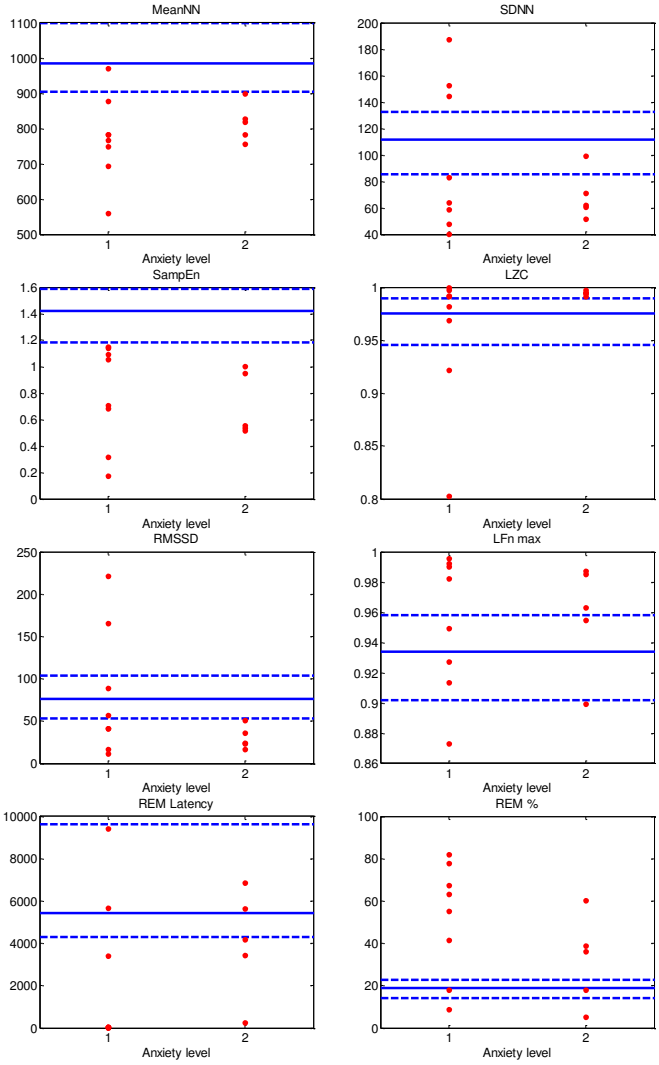

Fig. 3: Values of the most significant features grouped according to the anxiety level, compared with normality ranges.

V. CONCLUSION

This work, although regarding a limited set of subjects, shows some interesting results in the information content of HRV features in discriminating bipolar patients undergoing different clinical states from healthy subjects.

The results generally confirm what reported in literature: bipolar patients with strong levels of anxiety or in hypomanic or mixed state show lower HRV values, standard deviation [13, 14]. Also, reduced values of SDNN and RMSSD suggest a lower heart rate variability that may be related to an increased sympathetic drive on the heart.

Low values for SampEn in pathological subjects indicate a decreased HRV complexity, while the higher sympathetic activation in anxiety patients is expressed by the increased values of LFmax. Also, sleep parameters obtained by means of the automatic sleep staging allow for a significant distinction among healthy and pathological subjects, who present generally lower REM latency and higher REM%. This is true also for low anxiety patients and bipolar patients in euthymic state, and is confirmed by the work of Peykel et al. [15], which reports REM sleep anomalies as a residual symptom after remission in depressive subjects.

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