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An unexpected connection from our personalized medicine approach to bipolar depression forecasting

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Abstract. As one of the most complicated and recurrent depressive disorders, bipolar depression holds the highest morbidity and high mortality risk, but effective early detection and appropriately targeted treatments are still missing. This requires a new innovative approach, one capable of forecasting of mood states, in particular manic one. In our recent work, we combined several data sources to extract the most relevant variables, describe its intrinsic dynamics by network-flow analysis, and apply several supervised machine learning models to predict mania in BDD. By applying several methods of extracting and selecting the features from those aggregated data, and consequently performed supervised machine learning we arrived at real personalized medicine approach to BDD forecasting. Here we are interpreting previously unpublished data on sleep-related variables and its possible relation with irritability that was the most promising variable from daily self-report data. By putting this connection in the perspective of other recent neuroimaging and biochemical findings we are elucidating on another most important factor, namely the reason why some antidepressants shown to disrupt sleep dynamics can exacerbate the tipping point to mania, via the already mentioned link between sleep-related variables and irritability that our research demonstrated to be of most valuable predictable power.

Keywords: Bipolar depression, mood disorders, sleep-related variables, forecasting, personalized medicine.

1 Introduction

Bipolar depressive disorder (BDD) is a reccurent and complex mental disease which is considered to be one of the major contributor of worldwide work disability [1]. This disorder can produce everything from depression to mania (depression in major, dystimic or mixed forms), holds the most prominent suicide risk among mental disorders, usually starts in young adulthood and is characterized with high mortality risk [2-4].

The most important aspect of the treatment is medication, but BDD is usually misdiagnosed and treated as unipolar depression, in average for 8 years [5,6].
This is the reason why this mental disorder with very complex intrinsic dynamics needs new approaches to early and accurate detection, and this much sought soluiton is probably coming from the computational psychiatry.
In our recent work we aimed to mathematically describe the dynamics of and relationship between different phases, or states of the disease, by utilizing of network-flow analysis [7]. In this study, the variable "diagnosis" takes one of these 5 states (Depressed, Hypomanic, Manic, Mixed or Euthymic). By combining different sources we gathered data from conventional clinical interview, daily self-report via mobile application, recordings of smartwatches and actigraphs, and after careful selection of many variables (several methods of feature extraction and feature selection were used) we applied four supervised machine learning models: Random Forest, Decision Trees, Logistic Regression and Support Vector Machines algorithms. The final goal of our work was to discern what variables are most promising in predicting the mania, which has the most important practical implications [7,8]. That work was natural extension of our previous research on several manners of data collection and various possibilities of portable monitoring and measeurements, as well as various mobile applications used for self-report [9,10]. So, while we strived for reliable and relatable variables, we applied combination of previously succesfull pipeline that we used in other project of depression detection. Our aim to isolate the most relevant variables for mania prediction in BDD resulted in pinpointing irritability from daily self reports and duration of sleep as most promising [7].
Due to the nature of our previous publication and limitation of the space, we did not entirely discussed one group of variables that show to be in line with other research results coming from different disciplines dealing with the mechanisms and dynamics of bipolar depression: sleep related variables. Here we are offering previously unpublished data, that belong to our recently performed research on BDD, with additional interpretations and comparisons with other findings that connect those two variables that showed to be the most prominent in our work on BDD so far. In this manuscript we aim at elucidating on the connection between above mentioned most relatable variables, and putting them into a framework of overall effectiveness of BDD treatment.
This Manuscript proceeds with section 2 describing our Method, section 3 reporting our Results, and finally section 4 containing Discussion and the last section, Conclusions.

2 Methods

In our project Bip4Cast we collected the data from different sources and combined them to discern previously unknown connections and relations between them. Our sample was comprised of 17 BDD patients, who were in the program of treatment in a hospital (Nuestra Senora de la Paz, Madrid) with whom our University has a collaboration. After acquiring approval from the Local Ethics Committee, all the patients were interviewed and signed the informed consent to participate in this study. We used the data from the conventional clinical interviews, daily self-report via the mobile application, recordings of smartwatches and actigraphs, and after careful selection of many variables (several methods of feature extraction and feature selection were used) we applied, at the first stage, four supervised machine learning models: Random Forest, Decision Trees, Logistic Regression and Support Vector Machines algorithms. The results of this research are published in Llamocca et al., 2019 [10]. Further on a personalized model was developed by the same group of researchers in Llamoca et al., 2021 [7] and Portela et al 2021 [27]. In the last mentioned paper, the authors show how the emotional state of an individual *p* can be modelled as a function $m_p(t)$ on-time t for a specific patient *p*. The behaviour of this function fits well with alterations in the behaviour of the patient, while a regular behaviour of the patient is associated with a bounded behaviour of the function. Thus, $m_p(t) >> m_p(t+\varepsilon)$ on a specific time t for a small increase of time $t+\varepsilon$, indicates a rapid decline to a depressed state, maybe due to a sudden adverse event happening. On the contrary, $m_p(t) << m_p(t+\varepsilon)$, indicates a quick rise to a state of euphoria. Knowledge of the $m_p(t)$ function represents a great advance in personalized medicine. However, the model shows that this continuous function is a very complex function in which any approach is subjected to random events along to the daily life of a patient. To solve this problem, on one hand, discrete approaches have been applied. Psychiatrists use discrete indicators such as Young's indicator, used to measure manic emotional state and the Hamilton indicator, used to measure depressive emotional state. But these indicators are not very useful without a very frequent consultancy with the patient. On the other hand, the benefits of just a simple estimation of $m_p(t)$ are particularly relevant in patients with emotional disorders such as depression or bipolar depressive disorder. Some models can help the psychiatrist analyze the behaviour of $m-$function, and act accordingly to its values, for example, modify the patient's medication before a relapse occurs. A normal mood state is represented as a bounded value in an interval $(\alpha < m_p(t) < \beta)$, thus, if the value exceeds the maximum β, the emotional state reflects the direction of a manic state, while if the value is less than the minimum α, reflects deviation to the depression state. To make this decision possible, an estimation of the function must be calculated based on an array of measurable

characteristics (X_1, X_2, …, X_N), which characterize the mood state. Those variables have been previously studied in [7] and [27] as well as the proposal of the estimation as an ordered weighted average (OWA), that is

$$m_p(t) = \sum_{i=1}^{N} w_i X_{(i)}, \quad 0 < w_i < 1, \sum_i^N w_i = 1,$$

Where

$$\left(\forall i \exists! j: X_i = X_{(j)}\right) \wedge (\forall i \in \{1..n-1\}: X_{(i)} \leq X_{(i+1)}).$$

The aim was to extract the most relevant variables that are able to improve the forecasting of crises in BDD. Here we are focusing on N=4 sleep-related variables data that were gathered by the use of wearables, hence a real candidate for portable outpatient monitoring solutions.

3 Results

Our results show that among many variables collected, those relating to sleep in bipolar patients hold the most promising forecasting potential, that are also directly related to another most prominent variable belonging to another source of data (daily self-report), namely- Irritability.

Here we present four figures (Figure 1 to 4, below) that illustrate the changes of four different sleep-related variables over time, previously examined in another context in our recent publication [7]. This material is published for the first time here, since due to the very complex methodology, and space limitation of previous Journal we published just overall graphs depicting the changes in dynamics of all the patients. Here we present data about sleep-related variables for four of all BDD patients who participated in our study: P04, P06, P14 and P15. Those can serve as an illustration of how individual dynamics in BDD can significantly differ, and why its generalization in BDD might not be realistic. Just briefly, we describe the meaning of the variables present on the following Figures 1,2,3 and 4. Those variables we present here are:

(A) Sleeponset - the sleep starting time. This variable is in 48 hours format i.e. 01:00 am is expressed as 25 or 02:00 is expressed as 26.

(B) wakeup is the wake up time. It is in 48 hours format also.

(C) dur_spt_min is the duration of the sleeping period time expressed in minutes.

(D) sleep_efficiency is a variable between 0 and 1

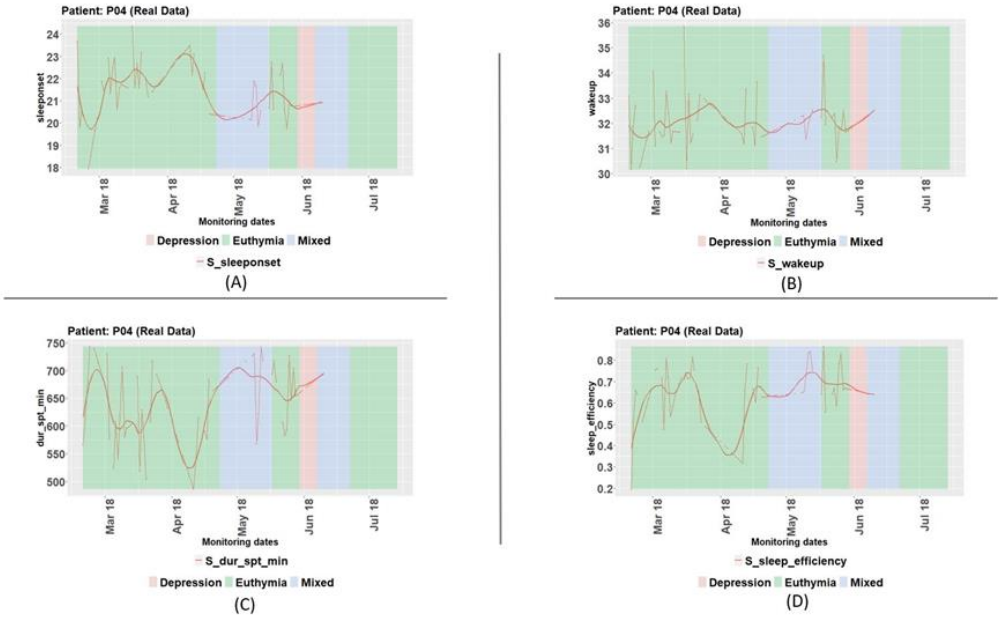

Figure 1: Graphical representation of four sleep variables detected in patient number 4 (P04). It seems this patient sleep better in Mixed states, while in Euthymic state patients' sleep efficiency shows a high variance.

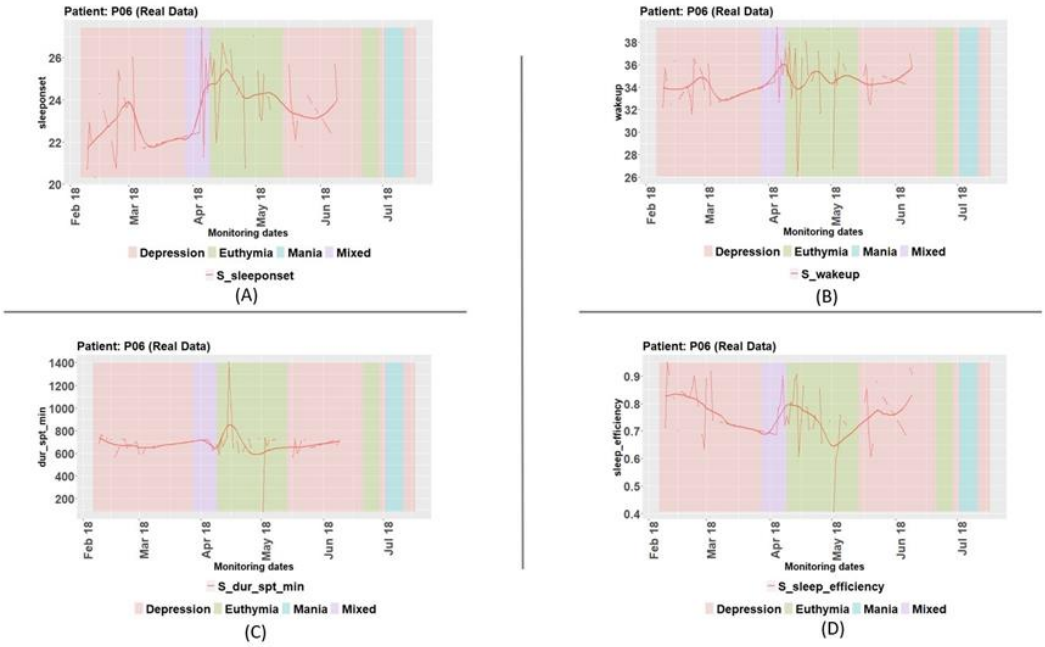

Figure 2: Graphical representation of four sleep variables changes over time in patient number 6 (P06). In general this person seems to sleep too much, which is characteristic of state of depression. In Depressed episodes the average sleep lasts for 11 hours (700 min). However, in Euthymic state sleep dynamics shows a high variance.

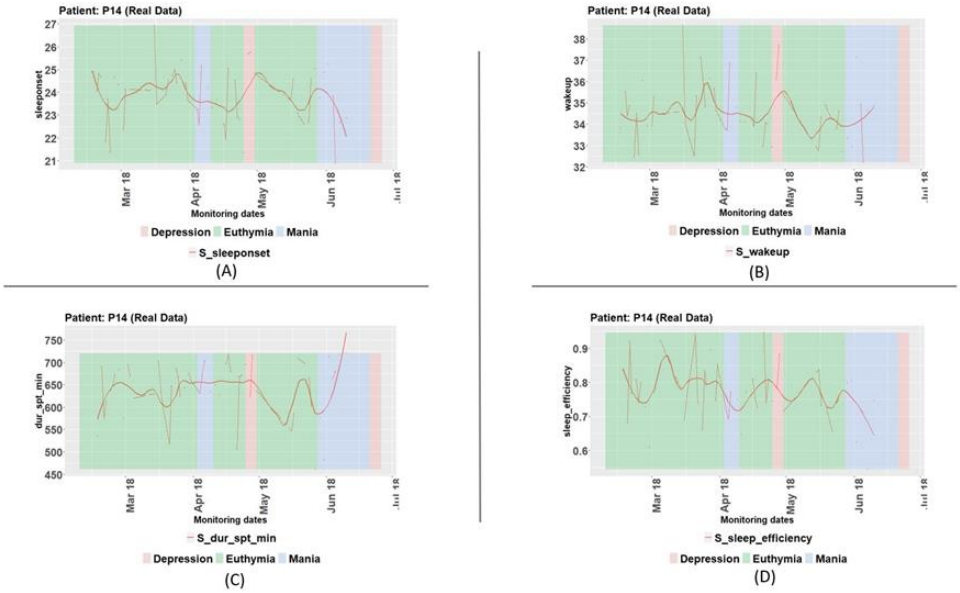

Figure 3: Graphical representation of four different sleep-related variables over time in patient number 14 (P14). The sleep efficiency seems to decrease in Manic episodes and it has a regular variance in Euthymic state.

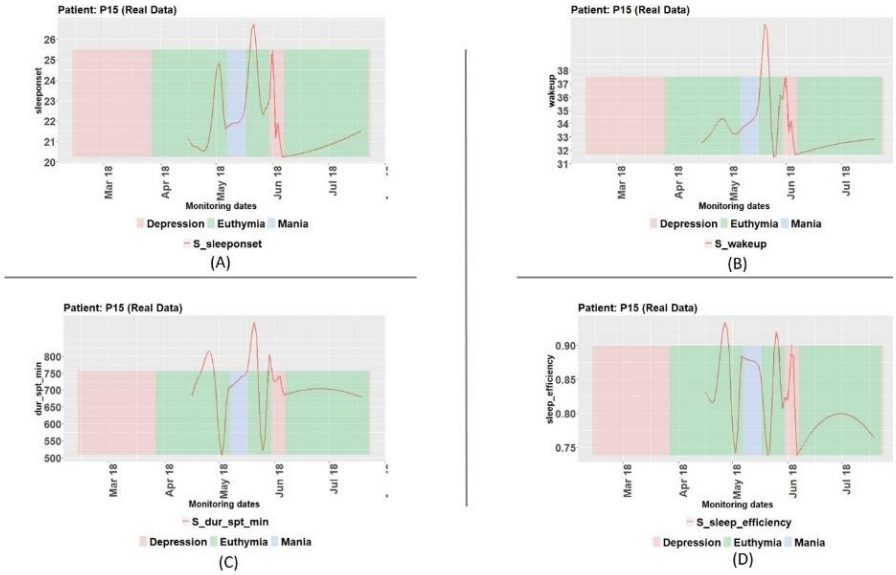

Figure 4: graphical representation of four sleep-related variables over time in patient number 15 (P15). This BDD patient seems to start sleeping before 10 pm in Manic episodes only. In Euthymic episodes patient seems to go to sleep later.

On all above presented figures for four different persons, the background of every graph are color-coded phases of the disease: Depression, Euthymia, Mixed and Mania, which were described as states in network-flow model from our prior publication [7]. These illustrate how every person's dynamics in the same time interval of collecting the data varies greatly; for example while one person spends significant amount of time in eythimia, other persons in the very same time interval passes through all possible states, even more than once.

All four figures (Figurese 1 to 4) contain the same variables and they are in the same order. However, we made different conclusion for each patient. Based on graphical representations, some conclusions could be:

As a conclusion for P04: It seems this patient sleeps better in Mixed states, while in Euthymic state patients' sleep efficiency shows a high variance.

As a conclusion for P06: In general this person seems to sleep too much, which is characteristic of state of depression. In Depressed episodes the average is 11 hour (700 min). However, in Euthymic state sleep dynamics shows a high variance.

As a conclusion for P14: The sleep efficiency seems to decrease in Manic episodes and it has a regular variance in Euthymic state

As a conclusion for P15: This BDD patient seems to start sleeping before 10 pm in Manic episodes only. In Euthymic episodes patient seems to go to sleep later.

Sleep –related variables showed to be most promising for prediction beside irritability variable from daily self-report [7-10].

4 Discussion

Our results show that even relatively small disruption of sleep (sleep duration, wakeup time, sleep efficiency) can lead to a tipping point for mania in bipolar depressive disorder (BDD). When sleep-patterns in a person widely vary from night to night, that usually leads to increased depressive symptoms.

Now, recently published data show that the disruption of sleep (sleep deprivation) is actually leading to the increase of serotonin 2a receptors response in brain [11]. From previous work we know that one night without sleep (unlike in healthy people) in bipolar depression patients can contribute to mania onset [12,13]. It is interesting to compare this with the research findings by Saad, Robillard and their colleagues [14,15] that demonstrated two important things for this phenomenon. Saad demonstrated that the changes of sleep characteristic for depression could be discerned from analysis of electrocardiogram (ECG) recorded during the sleep, probably due to its dependency on cortico-vagal control [16]. Robillard showed that antidepressants (SSRI in their study) are further aggravating the quality of sleep in depression patients who were taking them as a therapy, and even increasing the risk of apnea [15]. Knowing that the patients suffering from BDD are misdiagnosed and treated wrongly as unipolar depression patients in average for 8 years [5,6], this actually explain why the early discerning of the type of depression is so important. Although we started this research with forecasting mania in BDD as our primary goal, we realized that both early discerning of subtype of depression (unipolar vs bipolar) together with early screening for cardiovascular risk would be much more justifiable goal of our research, saving lives and increasing the span and quality of life of BDD patients.

By combining all of those findings from last decade, we can conclude that unexpected result from our work (since we aimed at forecasting mania based on portable devices data collection) is actually pointing to the direction of mismanagement of the treatment in BDD. We aimed at personalized medicine approach in BDD, but this particular part of our findings (sleep-related variables with a predictive value) show that there is probably a synergy there: antidepressants can further aggravate the sleep dynamics which in turn can more frequently lead to the onset of mania in BDD.

Although we are aware that personal dynamics of BDD widely differ from patient to patient (that actually makes BDD so hard to manage and to automate the detection), that also point to the direction of how urgent it is to discern bipolar from unipolar depression early; and that is not possible relying solely on current diagnostic practice, since it does not include objective markers in its standard diagnostic process.

Another possible conclusion from our previous work and literature review would be that we should urge clinicians to start using some form of early ECG screening in order to (very early in therapeutic process) discern whether the patient has bipolar or unipolar depression [17]. Also, since BDD patients are having 20-fold mortality risk in comparison to controls [3,18], an early screening to cardiovascular (CVD) risk, an increase of their mortality risk can be addressed in the same way. Also, Khandoker and colleagues demonstrated that even unreported suicidal thoughts are leading to singificnantly increased markers extracted from heart rate variability [28]. In cardiology, an early adopter of innovations in nonlinear analytic of ECG, an early screening for depression in patients surviving myocardial infarction is already a common practice, since it is known that those two risks combined are immensely increasing the mortality risk for a person [19]. Why not doing the similar early screening on CVD in psychiatry?

Pincus advised early in 2003 that relying on some form of irregularity statistics on EEG recorded during the sleep (since this state is very information-rich) in depression would yield accurate biomarkers knowing that physiology is obeying complex systems dynamics laws [20]. Glen and Moore showed that the time series analysis (2006) lead to accurate prediction of whether the BDD patient would go next to depressive or mania state, several weeks in advance [21,22]. Migliorini and colleagues (2012) showed on a small sample that nonlinear measures of ECG recorded during the sleep more accurately predicted the mood state than every day conventional clinical testing, in BDD known to have very complicated dynamics [23].

We showed that based on aggregated clinical data, daily self-report, and wearable measurements (smartwatches and accelerometers) that complicated dynamics can be mathematically described via network-flow model [7]. Contrary to unipolar depression that has two phases (episode and remission), BDD has five states (Depressed, Hypomanic, Manic, Mixed or Euthymic) with many intermittent phases and bidirectional flow (Llamocca et al., 2021). Based on the combination of data collected from BDD patients through wearable devices (smartwatches), daily self-reports, and medical observation at regular appointments, several feature extraction and feature selection techniques, plus four most popular supervised machine learning models, we arrived at personalized characterization of mood states in BDD. Contrary to other computational psychiatry methods applied in detection of unipolar depression (mostly major depressive disorder, MDD, for example [24,25]), we concluded that inter-individual differences in dynamics are requiring repeated analysis for each person; their personal dynamics were so different that that it would not allow for generalization. That showed to be a real personalized medicine (PM) approach [7].

Neuroimaging studies demonstrated that sleep deprivation cause disruption of communication within the mood control network in healthy people, who later reported increase in their irritability as a consequence [13]. Knowing that ‘irritability’ showed to be one of the two most promising predictive variables in our research [7,8], we

concluded that this particular connection between the two has even larger significance in forecasting in BDD. It is obvious that the disruption of sleep in bipolar depression patients can exacerbate already existing problems in mood circuitry, to the point of triggering the mania state. There are also an evidence that intentional sleep deprivation, due to above mentioned connection, hold a potential of therapeutic approach in BDD and other mood disorders [26].

Limitation of this study is that first of all, our original sample is small, but that is in reality problem with almost every psychiatric related study, where specially curated sample is very heard to find and access; we hope to reiterate this methodology on a larger curated sample which is planned to be collected within larger collaborative project during the year. Also, we could not relate it to healty controls, since monitoring healthy people without psychiatric symptoms was beyond the regulatory obstacels in this particular hospital. A typical involvement of a healthy student population to serve as control here makes no sense since only carefully curated sex and age-matched healthy control group might contribute to better conclusions (which was not possible in our case). Nevertheless we have significant conclusions that might have practicaly meaningful application in clinical practice.

To conclude, we suggest further research on larger datasets of this important connection between *irritability and sleep-related variables* in order to refine our forecasting methods to serve in clinical practice as real PM approach. Not only that our conclusions reported here can improve the early detection of mania, they can also be elaborated in the follow-up study to help improve the methodology of early detection of demonstrated connection between phase changes and quality of sleep and irritiability. We advocate that practicing psychiatrists and clinical psychologist who are working with BDD patients start applying regular screening of cardiovascular risk in their patients and apply heart rate variability analysis methods we found most useful in improving detection and prediction for better clinical decision making and overall effectivity of the treatment.

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