Pattern Discovery in an EEG Database of Depression Patients: Preliminary Results

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Abstract. *The ability to predict response to medication treatment of depressed patients, either early in the course of therapy or before treatment even begins can avoid trials of ineffective therapy and save patients from prolonged intervals of suffering. Symptom alleviation requires 4-6 weeks after starting current antidepressive medication. Based on the data basis of the patients and their EEG before and on the 7th day of treatment we apply data mining, causal discovery and machine learning approaches to discover interactive patterns between patient's brain regions to separate the treatment responders from non-responders. In this paper we report the preliminary results of our international project "Learning Synchronization Patterns in Multivariate Neural Signals for Prediction of Response to Antidepressants" ongoing at the University of Vienna, the Czech Academy of Sciences and the National Institute of Mental Health in the Czech Republic.*

Keywords: Major Depressive Disorder, Interactive Clustering, Granger Causality, Classification Methods

1. Introduction

Major depressive disorder (MDD) or clinical depression is a mental disorder characterized by low self-esteem, persistent sadness, and loss of pleasure in activities that are normally enjoyable. Modern antidepressant drugs have a response rate only up to 65% whereas the response requires usually 4-6 weeks to decide whether to continue with the treatment strategy or to change. The diagnosis of the disease is based on the person's experience, behavior, and mental status examination such as Montgomery-Åsberg Depression Rating Scale (MADRS). Medication treatment seems to be effective but mostly in patients with moderate to severe depression [3]. In comparison to epilepsy, in which seizure focus and/or events are represented by typical high-amplitude rhythmic epileptiform patterns in the EEG signal in corresponding brain areas, the EEG signal for MDD do not exhibit these explicit patterns. Having this in mind, we postulate that patients who have not responded to antidepressant treatment, may exhibit information patterns not within EEG trajectories but in the way how the brain regions temporarily interact with each other. To find these patterns and their differences for medication responders and non-responders, we explore the EEG databasis of MDD patients by methods of signal processing, interactive clustering, causal inference and machine learning.

2. Description of the Data Basis

The EEG data base used consisted of 176 patients, out of which 128 were females and 48 were males. These EEG recordings were acquired as a part of the study described in [2]. Every patient

ISBN 978-80-972629-7-6

was recorded before the start of anti-depression treatment and on the 7th day after the start of the treatment which lasted for around 4 weeks. Patients were recorded for 10 minutes, laying on a bed with elevated upper body at 30-45 degrees in a room with dimmed light with closed eyes (alerted when drowsiness appeared in EEG). Recordings from 19 standard electrode positions, namely, Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, and Pz, were used for analysis. The initial and the last 30 seconds of recordings were removed for each subject. For the task of interactive clustering, a subset of 134 patients were used and their EEG recordings pre-processed as described in [2]. For the task of classification of causal graphs, data from all the patients were used and pre-processed using the EEGLab toolbox [8] as follows. Since some patients' recordings were sampled at 1000 Hz and others at 250 Hz frequency, the recordings at 1000 Hz were subsampled to 250 Hz by taking every fourth sample. Further, the EEG was set to average reference and consequently band pass filtered from 1-40 Hz. In order to remove segments of data with artifacts, individual 2s segments of data were assessed and those segments which contain high-power artifacts in 20% or more of the considered channels were eliminated from the dataset.

In both data sets, each patient is assigned a label either 0 (non-responder) or 1 (responder) which was determined by psychiatric experts using MADRS score after the 4th week visit. In every experiment, we use the patients' EEGs from the 7th day of therapy or this EEG combined with the EEG before the therapy (day 0), ordered timely after each other.

3. Interactive Clustering

One way of finding patterns among the brain regions of patients is applying clustering on patients algorithm called interaction K-means (IKM) [6]. IKM models each subject as a multivariate time series, where the single dimensions represent the EEG signal at different electrode. In contrast to common clustering approaches, the cluster notion of IKM is based on the interactions between the univariate time series within a data object (patient). The objective is to assign objects exhibiting a similar intrinsic interaction pattern to a common cluster. A cluster is defined by a set of mathematical models describing the cluster-specific interaction patterns. To be able to separate patients into two clusters (responders and non-responders) by IKM, we performed exploratory analysis of the influence of preprocessing on the cluster purity (CP) of IKM on the EEG data set. To improve clustering accuracy of the algorithm on the given data we used sinusiodal, discrete wavelet transformation, z-normalization, exponential smoothing, Hilbert transform and Box-Cox transform, various distance metrics as well various subsets of electrodes (all 19 electrodes or electrodes in different hemispheres). The best clustering result with highest clustering purity $CP = 60.5\%$, was for the Box-Cox and z-score transformation (non-specific frequency band) in Euclidean distance for electrodes Cz, Fp1, F3, F7, C3, T3, P3, T5, O1.

Figure 1 illustrates the identification of electrodes P3 and T5 (the outgoing electrode of the arrows, in color green) as the most discriminative among the clusters. In the cluster of non-responders (left two), P3 and T5 were strongly related to the Fp1 and F3 electrodes, respectively. In the cluster of responders, P3 had strong relationships to the F3, Fp1, F7, and Cz electrodes, while T5 was strongly related to the O1 electrode. Based on the identified electrodes and their relationships within and between clusters, one may make some observations about the underlying neurological differences between responders and non-responders. We can hypothesize that the observed differences in electrode relationships between responders and non-responders may be related to underlying differences in neural connectivity or functional networks. Furthermore, the identified electrodes and their relationships may have clinical implications for predicting treatment response in depressed patients.

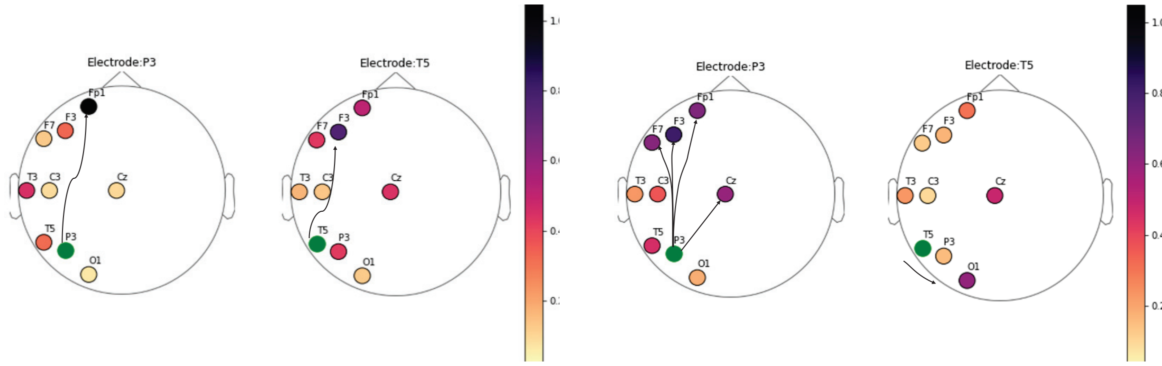

Fig. 1: Results of IKM with $CP = 60.5$. Left two heads are for the non-responders, right two ones for responders. Interactions w.r.t. electrodes P3 and T5 are visualized.

4. Granger Causal Graphs as Discriminative Patterns

Granger causality between two variables [4] as a temporal and computational concept of causality was extended to the case of $p \geq 2$ variables in terms of vector auto-regressive models with the lasso variable selection method [1] and is in literature called a graphical Granger model (GGM). To overcome the rate of false negatives of lasso, [5] used the so-called statistical minimum description length (MDL) principle to discover the Granger causal graphs with a high $F1$ precision.

A GGM among p Gaussian variables can be represented by a binary adjacency matrix A of size $p \times p$ where $A_{ij} = 1$ means that time series x_j is causal to x_i and $A_{ij} = 0$ that x_j is non-causal to x_i. Each row of A is computed by the criterion derived from stochastic MDL, more details can be found in [5].

5. Classification of Causal Graphs

Motivated by [2] that EEG structure of male and female patients may differ, we split the data set of 134 patients into male (31) and female (103) subjects. Classifiers were trained and evaluated separately for those two groups. Due to small sample of men we used 5-fold cross validation. The used classifier were: Support vector classifier with linear, RBF and polynomial kernels, k-nearest neighbor classifier, decision tree classifier, random forest classifier and naive Bayes classifier. We explored a number of different experiment settings: Hemisphere: left hemisphere (8 electrodes), left hemisphere with center electrodes (11 electrodes), or whole brain (19 electrodes); Frequency band: alpha band, theta band or the unfiltered data, i.e. in total nine different input data settings. Additionally, we applied a Box-Cox transformation to the input data before computing the causal graphs, in order to improve the normality of the data, required by GGM. On the training set consisting of only women, the best classification result was with a mean $F1 = 0.72$. On the training set consisting of only men, the best classification result on this data set was a mean $F1 = 0.86$.

6. Discussion and Future Work

Concerning the results achieved by the IKM clustering method, future studies could answer whether measuring activity in the discovered specific electrode locations could be used as a biomarker for predicting treatment response in depressed patients. Concerning the classification by the GGM causal graphs, the results still need to be validated on completely unseen data, using the test set that was previously set aside for this purpose. In addition to it, we will proceed in applying other data mining and machine learning methods on the data set. Concerning the applied classifiers to the GGM representation of patients we can conclude that there is a

ISBN 978-80-972629-7-6

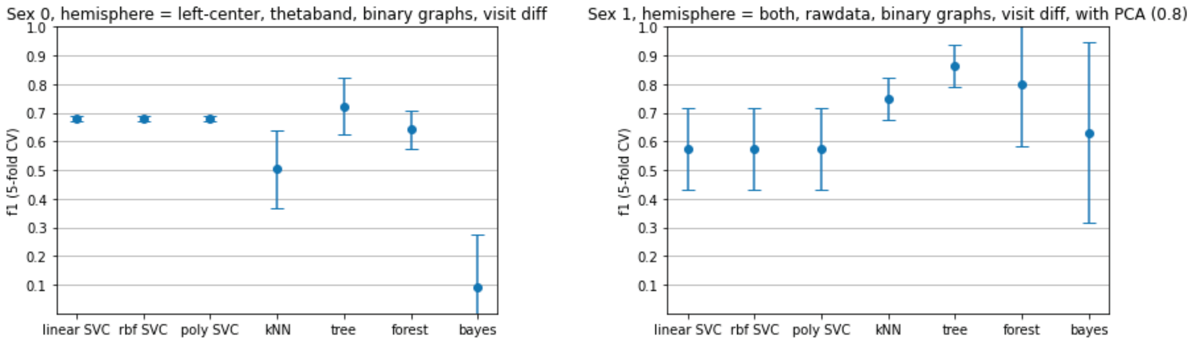

Fig. 2: Left: $F1$ for the left hemisphere of females with center electrodes on the theta band, using the difference between the GGM graphs as input. The best result is for the decision tree (DT) classifier. Right: $F1$ for the full brain of males on unfiltered data. PCA was applied to the input data, keeping enough components to explain 80% of the variance. The best result is for DT.

significant difference in precision among them and that for both separated sets (male, female), see Figure 2. Our results contradict to the opposite observations in the recent paper on a similar topic [7]. However, the size of the investigated data sets (different number of patients, a different duration of EEG monitoring and different feature extraction methods/representations) may play an important role in these contradictory observations.

Acknowledgements

This work was supported by the Czech Science Foundation GACR (Project No. GF21-14727K) and by the Austrian Science Foundation FWF (Project No. I5113).

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ISBN 978-80-972629-7-6