Resting-state global EEG connectivity predicts depression and anxiety severity

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***Abstract*— There is a recent interest in finding neurophysiological biomarkers which will facilitate the diagnosis and understanding of the neural basis of different psychiatric disorders. In this paper, we evaluated the resting-state global EEG connectivity as a potential biomarker for depressive and anxiety symptoms. For this, we evaluated a population of 119 subjects, including 75 healthy subjects and 44 patients with major depressive disorder. We calculated the global connectivity (spectral coherence) in a setup of 60 EEG channels, for six different spectral bands: theta, alpha1, alpha2, beta1, beta2, and gamma. These global connectivity scores were used to train a Support Vector Regressor to predict symptoms measured by the Beck Depression Inventory (BDI) and the Spielberger Trait Anxiety Inventory (TAI). Experiments showed a significant prediction of both symptoms, with a mean absolute error (MAE) of 8.07±6.98 and 11.52±8.7 points, respectively. Among the most discriminating features, the global connectivity in the alpha2 band (10.0-12.0Hz) presented significantly positive Spearman's correlation with the depressive (rho = 0.32, p_{FDR} <0.01), and the anxiety symptoms (rho = 0.26, p_{FDR} <0.01).**

***Clinical relevance*— This study demonstrates that EEG global connectivity can be used to predict depression and anxiety symptoms measured by widely used questionnaires.**

I. INTRODUCTION

Major depressive disorder (MDD) is the leading psychiatric disorder worldwide [1], and its symptoms include changes in cognition, reduced mood, interest or pleasure, and vegetative behavior [2]. The current diagnosis of depression is based on questionnaires that are susceptible to patient and clinician subjectivity [3]. Thus, the search for potential biomarkers aims to provide objective measurements about the stage of the disorder and consequently support diagnosis [3], [4].

The electroencephalography (EEG) is highly explored for the extraction of neural biomarkers. Some of the reasons are its high temporal resolution, which is fundamental to describe specific brain processes, as well as full availability and cost-effectiveness [4]. A widely explored EEG biomarker is the connectivity between channels measured by the spectral coherence [5]. However, a problem of this analysis is the choice of target-specific combination of channels, which can lead to confusing results. For example, while some studies describe MDD patients presenting reduced coherence values in theta, alpha, and beta bands compared to healthy controls [6], [7], [8], [9], others groups report the opposite effect at the same bands [10], [11].

Instead of location-specific connections, a new concept in neuroimaging is the evaluation of whole-brain connectivity for understanding neuropsychiatric illnesses [12]. For example, studies evaluating resting-state whole-brain connectivity in functional magnetic resonance imaging (fMRI) fMRI of MDD patients showed abnormal patterns compared with healthy controls [13], [14], which leads to accuracies higher than 90% in binary classification experiments [15]. A notable aspect of whole-brain connectivity is the consistency across imaging modalities [16]. Thus, in addition to the previously reported channel-specific connectivity in EEG, it is expected that the evaluation of whole-brain connectivity in EEG data would provide similar results to those previously reported using fMRI data.

Herein, support vector regression (SVR) was combined with whole-brain coherence analysis (global connectivity) of EEG data to predict depression severity. This is the first experiment combining SVR and global EEG connectivity and may provide objective measures of symptom severity to identify subgroups of patients.

II. EXPERIMENTAL METHODS

A. Subjects

The dataset used in this study is composed of EEG signals recorded from participants with MDD and healthy controls. This is an open database publicly available at the PRED+CT website [17], and previously reported by Cavanagh et al. [18]. From the original dataset of 121 subjects, 2 participants were not included in the present study due to missing triggers or other experimental data. Thus, the final sample contains 119 subjects (18.86±1.19 years, 72 females), including healthy and depressive participants. The average and standard deviation scores were 9.35±10.50 for the Beck Depression Inventory (BDI) [19], and 40.25±13.50 for the Spielberger Trait Anxiety Inventory (TAI) [20].

B. EEG acquisition and preprocessing

Briefly, signals were recorded using a Synamps2 system (Neuroscan), with 500 Hz sampling frequency and referenced to the central channel between Cz and CPz. Electrode positions followed the 10-20 International System, including Fp1, Fpz, Fp2, AF3, AF4, F7, F5, F3, F1, Fz, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FCz, FC2, FC4, FC6, FT8, T7, C5, C3, C1, Cz, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CPz, CP2, CP4, CP6, TP8, P7, P5, P3, P1, Pz, P2, P4, P6, P8,

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PO7, PO5, PO3, POz, PO4, PO6, PO8, O1, Oz, O2, as well as two electrodes on the mastoids, and two EOG channels (for more details about the signal registration, please refer to the original paper - [18] - and the repository - [17].

All EEG channels were initially band-pass filtered (0.5 to 50 Hz) with a second-order Butterworth filter. Then, each channel was re-referenced to linked-mastoid reference, and detrended by the average signal. Although an eyes-closed condition provides a reduced amount of eye movement artifacts, it's still expected the presence of slow-frequency movement artifacts [21], and muscular artifacts caused by moments of forced eye-lids closure [22]. Thus, artifact correction was performed using the wavelet-enhanced independent component analysis (wICA) method [23] with the cleaning artifact threshold set to 1.25, and the independent component artifact detection threshold set to 4 [24]. Later, signals were segmented into 18 non-overlapped epochs of 8 seconds corresponding to periods of resting-state with eyes closed.

C. Connectivity analysis and support vector regression

Temporal series from all channels were decomposed into six spectral bands, namely: theta (4.0-8.0Hz), alpha1 (8.0-10.0Hz), alpha2 (10.0-12.0Hz), beta1 (12.0-20.0Hz), beta2 (20.0-30.0Hz), and gamma (30.0-50.0Hz). Delta band was not included in this analysis due to the influence of the wICA filtering in this frequency. The sub-divisions of alpha and beta are justified by different spectral distributions associated with the default-mode network (DMN) in the lower and higher portions of these bands [25]. For each EEG band, the connectivity between two channels was measured by the magnitude squared coherence [5], using 2.5 s moving-windows and 90% of overlap between successive windows. A Fisher's z-transformation was applied to these values to assume a normal distribution [26]. After that, values were averaged across epochs into a single value for each pair of channels. All possible combinations of channels were used to generate a connectivity matrix of 60x60 dimensions per frequency band. Finally, the lower triangular matrix was summed and averaged across epochs, resulting in one global connectivity value per frequency band per subject.

Support vector regression (SVR) with linear kernel [27] was applied to predict depression (BDI) and anxiety (TAI) symptoms based on the global connectivity in different EEG bands. The symptom predictions were carried out using the leave-one-subject-out (LOSO) cross-validation technique. The accuracy was measured by the mean absolute error (MAE = observed score minus predicted score), and the Spearman's correlation between the observed and predicted scores. Resulting p-values were FDR corrected for two comparisons. However, it is essential to mention that these p-values are only approximated, once the exact null distribution in leave-one-out procedures is unknown [28]. Finally, the relevance of each band was quantified by using the mean absolute weights assigned for each EEG band in the LOSO process [29].

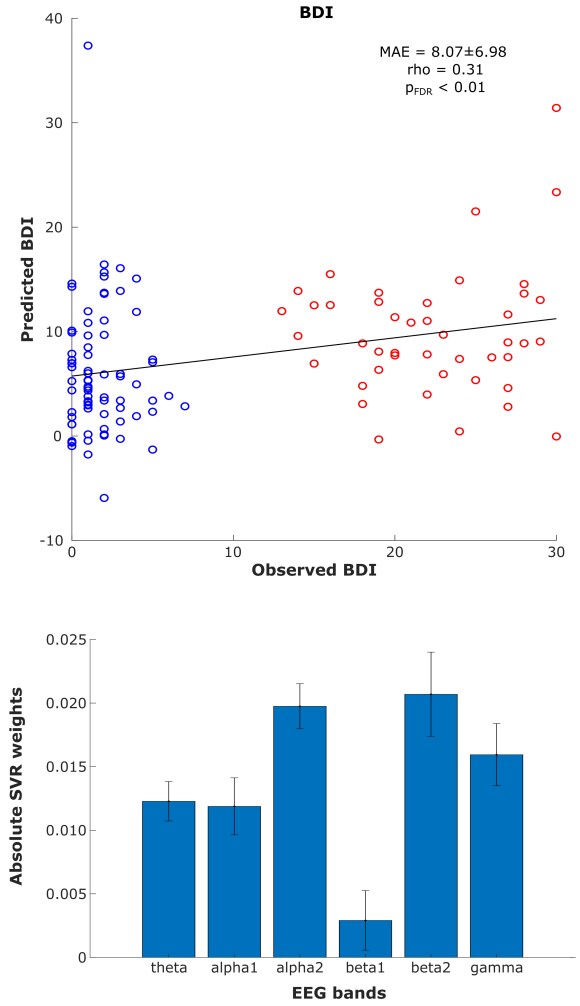

Fig. 1. (A) BDI score prediction based on global EEG connectivity. Blue dots show healthy subjects (BDI<10) and red dots represent depressive patients (BDI>13). (B) Absolute weights attributed by the SVR.

III. RESULTS

Figures 1 and 2 show scatter-plots of predicted values and observed BDI and TAI scores, respectively, as well as the relevance of each EEG band according to the SVR. In both charts, healthy subjects (BDI<10) are plotted in blue and depressive patients (BDI>13) in red. The mean absolute error (MAE) was 8.07±6.98 points for BDI scores (the scale range is from 0 to 63 [19]), with the Spearman's correlation coefficient between predicted and observed scores equal to 0.31 ($p_{FDR} < 0.01$). For TAI scores, the MAE was 11.52±8.78 (scale range = 20 to 80 [20]), with Spearman's correlation equal to 0.20 ($p_{FDR} < 0.03$).

Among the frequency bands, alpha2 and beta2 were considered the two most informative features when predicting BDI scores, while alpha 2 and beta1 were the most relevant for TAI score prediction. Post-hoc Spearman's correlation analysis show that alpha2 (rho = 0.32, $p_{FDR} < 0.01$), but not beta2 (rho = 0.10, $p_{FDR} < 0.30$), is significantly correlated with BDI scores. For TAI scores, both alpha2 (rho = 0.26,

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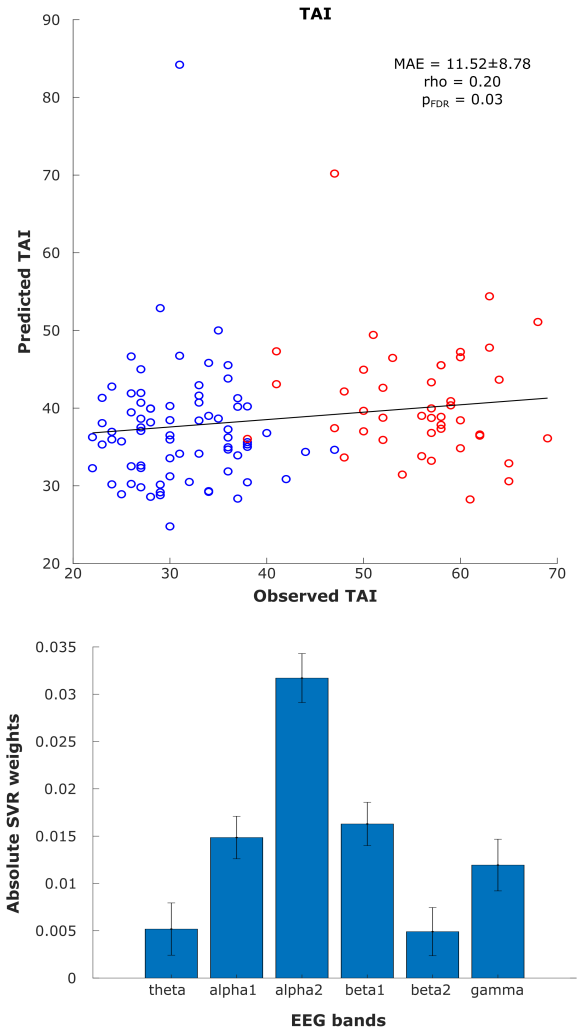

Fig. 2. (A) TAI score prediction based on global EEG connectivity. Blue dots represent healthy subjects (BDI<10) and red dots show depressive patients (BDI>13). (B) Absolute weights attributed by the SVR.

$p_{FDR} < 0.01$) and beta1 (rho = 0.20, $p_{FDR} < 0.03$) showed significant correlation with the reported scores.

IV. DISCUSSION

A. Methodological considerations

Herein, we predicted depressive and anxiety symptoms using global EEG connectivity. The idea of using regression methods is different from studies using binary classifiers to discriminate MDD patients from controls [30], MDD patients from other illnesses [31], or to predict treatment outcomes [32], [33]. This approach gives the possibility of identifying neurobiological biomarkers that predict continuous variables [27], such as symptom severity in different scales. This aspect is especially relevant in disorders such as MDD since it presents heterogeneous symptoms [34] and comorbidity with other psychiatric illnesses [35]. Additionally, the evaluation of this methodology using a publicly available dataset allows the replication of these results by other researchers, and the comparison with future approaches using this database.

B. Relevant features

Different from non-linear methods, a linear kernel allows the quantification of the contribution of each EEG band for obtaining the predicted values [29]. In this study, despite the evident contribution of many frequency bands to the prediction of symptom severity, the features that contained the most relevant information were in the alpha and beta bands. In both cases, these features presented positive correlations with the symptom severity, which is consistent with previous studies reporting augmented coherence in these bands in MDD patients [10], [11]. Also, the EEG alpha band seems to be positively correlated with Spielberger trait anxiety [36].

This paper evaluated the global EEG connectivity instead of using biased a priori definition of regions of interest. This is relevant as predictive information for depressive and anxiety symptoms might be sparsely distributed in cognitive networks, instead of located in specific areas. For example, the distribution of EEG alpha and beta frequencies over the scalp during eyes-closed resting-state is associated with the DMN [25], [37], [38]. In depressive patients, this is a relevant finding since they tend to present rumination and brooding symptoms, causing a higher attachment to the DMN in comparison to other cognitive networks, as the salience detection network [39].

C. Limitations and ongoing investigations

Notwithstanding, given that a considerable number of subjects scored zero in the observed BDI, this finding should be interpreted cautiously due to zero-weighting issues [40]. This bias might also explain the fact that some of the BDI predictions were below zero. Also, this dataset does not have patients with severe depression (BDI > 29), or subjects in the interval $10 <$ BDI < 13 [19]. Thus, it was not possible to explore whether global EEG connectivity may reliably predict symptoms' severity of different subgroups of depression [2]. Future experiments should include patients in these ranges, as well as try to evaluate if these results are consistent in other widely used depression and anxiety scales. Future studies also shall consider feature selection methods to identify the most relevant connections, for example, using the connectome-based modeling method [41] as a selector of relevant attributes.

V. CONCLUSIONS

In this paper, a new method for EEG-based prediction of depressive and anxiety symptoms is proposed. We evaluated the global EEG connectivity in a multi-channel EEG database measured from 119 participants (44 MDD patients and 75 controls). Our results show that a support vector regressor can achieve a significantly accurate description of depressive symptoms from the Beck Depression Inventory and anxiety symptoms from the Spielberger Trait Anxiety Inventory. The predictive tool has the potential do assist psychiatrists in MDD diagnosis, as well as in providing valuable information regarding the neural basis of this disorder.

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