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Identification of Neuropathic Pain Severity based on Linear and Non-Linear EEG Features

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Abstract— **The lack of an integral characterization of chronic neuropathic pain (NP) has led to pharmacotherapy mismanagement and has hindered advances in clinical trials. In this study, we attempted to identify chronic NP by fusing psychometric (based on the Brief Inventory of Pain – BIP), and both linear and non-linear electroencephalographic (EEG) features. For this purpose, 35 chronic NP patients were recruited voluntarily. All the volunteers answered the BIP; and additionally, 22 EEG channels positioned in accordance with the 10/20 international system were registered for 10 minutes at resting state: 5 minutes with eyes open and 5 minutes with eyes closed. EEG Signals were sampled at 250 Hz within a bandwidth between 0.1 and 100 Hz. As linear features, absolute band power was obtained per clinical frequency band: delta (0.1~4 Hz), theta (4~8 Hz), alpha (8~12 Hz), beta (12~30 Hz) and gamma (30~100 Hz); considering five regions: prefrontal, frontal, central, parietal and occipital. As non-linear features, approximate entropy was calculated per channel and per clinical frequency band with addition of the broadband (0.1~100 Hz). Resulting feature vectors were grouped in line with the BIP outcome. Three groups were considered: low, moderate, and high pain. Finally, BIP-EEG patterns were classified in those three classes, achieving 96% accuracy. This result improves a previous work of a SVM classifier that used exclusively linear EEG features and showed an accuracy between 87% and 90% per class to predict central NP after spinal cord injury.**

I. Introduction

Currently, the management of chronic neuropathic pain (NP) remains a challenge. The reason is poor characterization [1], because it is based almost exclusively on the subjective perception of the patient, given through written or verbal reports. This has hindered an accurate clinical management of NP patients [2]. The International Association for the Study of Pain defines NP as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" [3]. When NP lasts over three months, it becomes chronic, and neurons from the central nervous system (CNS) respond with neuroplastic changes. However, the CNS will respond and evolve to NP differently in view of genetic, environmental, emotional or cognitive factors [4]. Chronic NP is a worldwide public health issue, affecting 7-10% of the adult population, wherefrom 6% are infants, and 35% are oncological patients [5]. In pediatric patients, NP management and characterization becomes even more challenging because verbalization is limited [6]. Seventy physicians were interviewed from public and private care units across Mexico [7], which has approximately 4.5 million individuals with chronic NP. As a result, they found that first-line treatments were heterogeneous and unstandardized. In a recent study undertaken in Germany, 57% of the total patients with chronic pain had NP, but only 18% of those patients received adequate pain treatment in terms of dosage or number of pharmacological agents used [8]. Moreover, only 40-60% of patients have obtained sufficient pain relief with medications given in combination or alone; including the universal used pregabalin and gabapentin are ineffective for most patients with NP [9]. Recent NP pharmacological clinical trials have failed to provide efficacy, even when they have increased, owing to the lack of proper characterization and stratification of NP [10]. However, NP is not only an abstract perception, but an electrophysiological signal modulated by neurotransmitters and synapses, which can be quantified and interpreted. To quantify NP, it then seems necessary to consider both psychometric testing (the patient report) and electrophysiological measurement (neuronal plastic changes of the electrical activity of the CNS). In the light of the above discussion, the aim of the present work is to investigate if NP is identified by patients' reports collected by applying the Brief Inventory of Pain (BIP), along with the analysis of the electroencephalographic (EEG) activity to identify their level of pain. To our knowledge, only one study [11] has classified NP based on EEG features. In [11], EEG band power in eyes open (EO) and eyes closed (EC) condition were used as features, and a support vector machine (SVM) as classifier. Their pattern recognition proposal achieved 87-90% of classification accuracy. Our hypothesis is that including non-linear EEG features can increase classifier performance due to the better characterization of neurophysiological attributes of NP, and having in mind that disease identification in clinical applications should be closer to 100% [11].

In this study, approximate entropy (ApEn) was used as the measure of non-linearity for its clinical applications concerning biological signals. The development of ApEn was motivated by data length and noise constraints commonly encountered in heart rate, EEG, and endocrine hormone secretion data sets [12]. Thus, ApEn is relatively unaltered by noise, it is finite for stochastic, composite and noisy deterministic processes [13], and it detects changes in subjacent episodic behavior undetected by peak amplitudes [14]. Recently, EEG signals analyzed with ApEn have effectively predicted between control and neuropathological conditions, such as: depression [15] and epilepsy [16]. On this evidence, this investigation sought to improve the identification of NP severity by including non-linear EEG features using ApEn, in previous tested pattern recognition proposal [11] based on linear features and linear classifiers.

II. Methods

A. Sample

The sample size was calculated considering the mean individual alpha frequency of healthy individuals ($p0=10$ *Hz*

[17]*),* and that of NP individuals (*p1* = 9.5 Hz [13]), with a standard deviation of 1. A two-tailed normal distribution (z) with an alpha significance level of 0.05 and a power between 0.8 and 0.9 was selected, resulting in a sample size between 32 and 43 patients. Therefore, 35 chronic NP patients (8 men and 27 women) with a mean age of 44 ±13.98 were recruited for this study. None of those reported a severe mental disease, neurological disorder (beside NP), previous head trauma, cerebral infarct, or CNS tumor. To be eligible for the study, all participants completed the Pain Detect questionnaire. Noneligible patients were all of those who obtained a score less than 12 (in a range between 0 and 38). The questionnaire outcome was confirmed by the clinical history of the patient. Patients were asked to list their medications taken in the last 24 hours before the EEG recording. Twelve patients (n=12) were not taking any type of medication, eighteen patients (n=18) were taking centrally acting drugs for over a year, two patients (n=2) were on cannabidiol derivatives, and three (n=3) took nonsteroidal anti-inflammatory drugs for pain attacks. The effects of centrally acting drugs have been proved to be of secondary relevance since there were no differences found in the global power of NP patients with or without central acting medications [18]. The causes for NP in the studied population were spinal cord injury (31%), peripheral neuropathy (23%), diabetes (17%), trigeminal neuralgia (9%), CNS disorder (6%), and other (14%). All patients signed a written informed consent according to the world medical association declaration of Helsinki and were granted monetary remuneration. This study was approved by the Clinical Investigation Ethics Committee of TecSalud with the following number: P000369-DN-RespElectro-CI-CR005.

B. Questionnaire-based Monitoring

Two questionnaires were applied: (a) Pain Detect, and (b) BIP. The first was chosen to confirm the presence of NP and was applied before the recording session, whereas BIP was applied at the beginning of the EEG recording session. BIP quantified the level of pain and identified the interference level in daily activities according to individual experiences of pain.

C. EEG Recordings

Ten minutes of spontaneous EEG recording were acquired using 22 electrodes positioned according to the standard 10/20 international system. The amplifier in use was the Smarting mBrain. OpenViBe software was used to implement the experimental paradigm and record the EEG signals. The sampling frequency was 250 Hz, and the bandwidth was between 0.1 and 100 Hz. Electrode impedances were kept below 5 kΩ. Right and left mastoid electrodes were used as references and Cz as the ground electrode. Patients sat in an upright position. The first 5 minutes, they were asked to keep their eyes opened and fixed on a white cross in a dark background of a monitor 50 cm away. At the end of the first 5 minutes, the cross disappeared, and patients closed their eyes for the last 5 minutes until a beep marked the end of the recording.

D. Signal Analysis

Signal Preprocessing. EEG raw signals were preprocessed using EEGLAB toolbox (v.19.1.1) of MATLAB (R2020a) software. Signals were filtered first by a 6th order Butterworth high-pass filter with a cut-off frequency set at 0.1 Hz to remove very low frequency artifacts. Then, transitory artifacts were rejected using the Artifact Subspace Reconstruction [19]. After that, muscular, ocular, cardiac, line noise, or channel noise artifacts were removed by Independent Component Analysis supported by ICLabel [20].

Feature Extraction. To estimate the level of neuronal oscillations, a linear and non-linear method were applied to 1-min segments (60s x 250 Hz, N=15000) of the recorded 10-min signals. First, segments were filtered into the five clinical frequency bands and the broadband. Six filters were designed for ApEn, whereas only five were used for power. The filters were 8th order bandpass filters with the lower and higher frequency of each band specified as follows. On one hand, ApEn was calculated for the 22 electrodes and for six frequency bands: delta (0.1~4 Hz), theta (4~8 Hz), alpha (8~12 Hz), beta (12~30 Hz), gamma (30~100 Hz) and broad band (BW) (0.1~100 Hz). On the other hand, absolute band power was calculated for five bands (delta, theta, alpha, beta, and gamma) and for the following five regions, averaging the EEG electrodes over each region: prefrontal (AFz, Fp1, Fp2), frontal (F7, F3, Fz, F4, F8), central (T7, T8, C3, C4, Cz, CPz), parietal (P7, P3, Pz, P4, P8), and occipital (POz, O1, O2).

Absolute band power was calculated to estimate the level of neuronal synchrony according to (1),

$$y[n] = \frac{1}{N}\sum_{i=1}^{N} x_i^2[n] \quad (1)$$

where n is each data point of N (the 1-min segment, N=15000) and x is the amplitude value of the filtered signal. ApEn was obtained to measure the regularity of a non-linear time series with the Predictive Maintenance Toolbox [21]. ApEn measures the likelihood that runs of patterns that are close of *m* observations remain close on next incremental comparisons. Thus, two input parameters are needed: the pattern length *m,* and similarity criterion *r* that is used to identify the meaningful range in which fluctuations in data are similar [22]. Thus, the ApEn was calculated as $approxEnt = \phi_m - \phi_{m+1}$ in line with (2),

$$\phi_m = (N-m+1)^{-1}\sum_{i=1}^{N-m+1}\log(N_i) \quad (2)$$

The parameter *m* is obtained by reconstructing the phase-space. This is done by delay-coordinate embedding in a higher dimensional space for the uniformly sampled univariate time signal. Hence, the time series is reconstructed according to (3) [23],

$$X_{1,i}^{r} = \left(X_{1,i}, X_{2,i}, \ldots X_{1,i+(m_1-1)\tau_1}\right), i = 1, 2, \ldots, N-(m_1-1)\tau_1 \quad (3)$$

where X is the 1-min segment, N is the length of the time series (600s*250 Hz), τ_1 is the delay (i.e., lag) for embedding, and m_1 is the embedding dimension for X_1. To compute the delay for reconstruction, the delay is set to the first local minimum of AMI. AMI is computed as (4) [23],

$$AMI(T) = \sum_{i=1}^{N} p(x_i, x_{i+T}) log_2\left[\frac{p(x_i,x_{i+T})}{p(x_i)p(x_{i+T})}\right] \quad (4)$$

where N=15000 the length of the segment, and T=1: MaxLag. The resulting delay differed depending on the subject or condition. Computing the delay in this manner (i.e., per segment), ensured that successive components of the reconstructed state vectors were neither redundant or uncorrelated [24]. The embedding dimension was estimated using the False Nearest Neighbor (FNN) algorithm [25]. For a point *i* at dimension *d,* the points X_i^r and its nearest point

X^{r*}_i in the reconstructed phase space $\{X^{r*}_i\}, i = 1{:}N$, are false neighbors if (5),

$$\frac{\sqrt{R_i^2(\mathrm{d}+1)-R_i^2(\mathrm{d})}}{R_i^2(\mathrm{d})} > DistanceThreshold \quad (5)$$

where $R_i^2(\mathrm{d}) = \| X_i^r - X_i^{r*} \|^2$ is the distance metric. When results were computed, dimension was $m=3$ for all NP patients in EO and EC, which agrees with the theoretical implications of [26]. Previous references [24], held that EO had an increased dimension than EC, but it wasn't the case for this study. The reason for dividing the 10-min segments in 1-min segments, was done according to [27] which states that the optimal number to estimate m depends on the data points per segment, which should range between 10^m and 30^m. The number of within range points at point i was calculated by (6),

$$N_i = \sum_{i=1, i\neq k}^{N} 1(\| Y_i - Y_k \|_\infty < R) \quad (6)$$

where one is the indicator function, and R is the radius of similarity (i.e., r, the similarity criterion), r was calculated as 0.2*variance(X), where X is the 1-min segment of a specific channel and subject in either EC or EO. These values have been demonstrated to produce good statistical reproducibility for time series of length N > 60 [28]. Normalizing r with this approach gives ApEn a scale invariance, so it is not altered by uniform processes of magnification, reduction, or constant shifting to higher or lower values [13]. As a result, 157 features ([22 electrodes × 6 bands] + [5 regions × 5 bands]) were extracted, yielding 350 observations (35 patients × 10 EEG segments). The dimensionality of the resulting feature vector was 157. Finally, data were normalized in z-score with center 0 and a standard deviation of 1.

Classification. The feature vectors were labelled according to the severity of the actual pain reported in the BIP. Three classes were considered: (a) low pain = 0 – 3, (b) moderate pain = 4 – 6, and (c) high pain = 7 – 10. For feature selection, the number of features for power was reduced in the preprocessing stage by averaging the 22 electrodes across regions based on the relevance that certain brain regions have on the mechanisms of neuronal oscillations. Also, feature selection was incorporated in the classifier itself during the training phase using the kernel functions. As classifier, a SVM with a quadratic kernel function was selected. To classify the three classes, one versus one was used as multiclass method. To validate the performance of the model, a cross-validation of 5-Fold (k=5) was implemented. Data were divided into 5 randomly chosen folds of roughly equal size. One subset was used to validate the model trained using the remaining subsets. This process was repeated 5 times such that each subset was used exactly once for validation. The average error across all the 5 partitions was reported as ε.

E. Statistical Validation

After proving normality with Shapiro test, a one-way ANOVA test was carried out in R (version 1.2.5033) to test if the differences between group means were statistically significant. Pain severity (low, moderate, and high) was considered the factor variable. Afterwards, a Tukey test was performed to test the significance between all pairs of means

III. Results and Discussion

To give an insight into the EEG characterization of NP based on linear (absolute band power) and non-linear (ApEn) features, the two most differentiable features among the three classes are presented. These tendencies can help us explain the trends of the abnormal increased neuronal synchrony/irregularity expected from plastic changes owing to the different NP severity levels. The first five ranked features for the classification of NP severities are shown in Fig. 1.

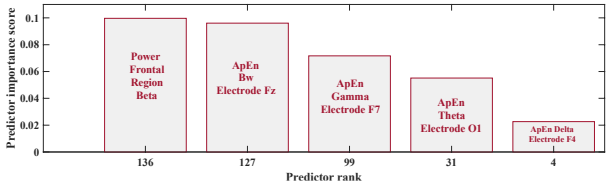

Figure 1. Predictor importance scores of the first five ranked features of the classifier using the minimum redundancy maximum relevance algorithm [29].

A. The most differentiable feature: Beta Band Power

The most differentiable feature among the classes was beta band power over the frontal region. This finding is in line with the findings of [11], where beta band features provided the best separability for the group of chronic NP from three other groups ((1) controls, (2) patients that developed NP within six months of EEG recording, and (3) patients that did not develop NP within six months of EEG recording) from a sample of 31 subacute spinal cord injury patients. Besides, other studies have reported increased beta oscillations in frontal brain areas and centro-parietal regions which correlate positively with the pain matrix [18], [30]. In this study, throughout all levels of pain in the EC condition, there was an increased power located in the central region (T7, T8, C3, C4, Cz, CPz), which also supports the findings related to the pain matrix as mentioned above. Furthermore, beta has been recognized as a characteristic oscillation in chronic pain, because it provides prediction signals via descending feedback connections, which hold the theory that chronic pain arises from prediction errors rather than nociceptive input [31]. For the beta band, the lowest power (-0.631) was reached in the parietal region for the EO condition in the low pain group. The highest power (0.732) was found in the parietal region of beta band for the EC condition in the high pain group. Enhanced attention to the inward perception of pain is probably responsible for this increased power since attention boosts the prediction error [32]. When patients open their eyes, the attention is withdrawn from the interior pain percept to outward stimuli.

B. The second most differentiable feature: Approximate Entropy

The second most differentiable feature among the classes was ApEn in the BW (0.1 – 100Hz) for the Fz electrode (see Fig. 5 for feature distribution in this electrode). In Fig. 2, the average ApEn across the 35 participants in the 22 channels is presented.

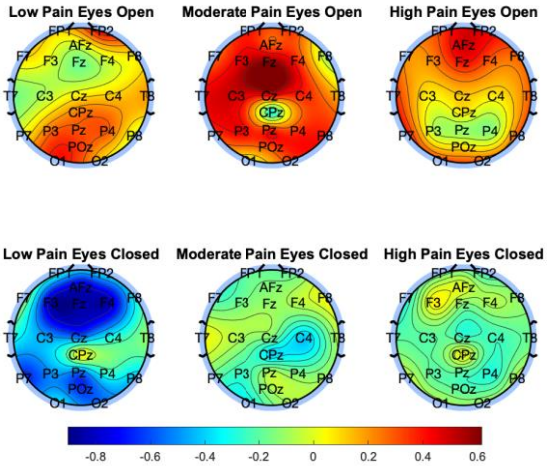

Figure. 2. Average ApEn of the 35 participants stratified according to the severity of their pain. Note that values are normalized in line with a z-score scale.

It could be proposed that absolute band power is inversely proportional to ApEn since band power increases when the level of synchronized neuronal activity increases as well. In contrast, ApEn decreases when the regularity of EEG signals increases, that is, the neuronal synchronicity. As a result, in the BW, ApEn reached the highest value in moderate pain for the AFz electrode in EO condition (ApEn = 0.586), and the lowest value for the low pain group with EC condition in F3 electrode (ApEn=-0.86). By inspecting Fig. 2, it seems that the irregularity of neuronal activity moves from posterior to frontal brain areas as pain increases. This argument may be sustained by the two opposing roles of the prefrontal cortex in pain: (a) the location where top-down processing modulates pain in the dorsal horn to the CNS, and (b) the area where induction of pain chronicity occurs [33]. Also, the prefrontal cortex is related to the proper psychological and physical therapeutic management of chronic pain given its close relationship to emotional processing and executive behavior [34]. For moderate pain, there is an overall increased ApEn in most parietal, central and frontal electrodes, with the highest ApEn localized between the frontal and central electrodes. This generalized enhanced ApEn may be attributed to the different processing centers when NP is not at its highest, given that observed changes in EEG power in NP may also be widespread and correspond to multiple changes in an interconnected network of somatosensory, limbic and associative structures [35]. The increased irregularity for the occipital lobe in low pain may be due to the suppression of resting state occipital alpha-rhythm, which occurs in NP [36].

C. Differentiation among NP severity levels: Classification outcomes

In Fig. 3, the resulting confusion matrix of the 3-classes SVM-based classification is presented. As can be seen, the 3 levels of NP severities were identified at least in a 93% and misclassified at most 6%. In Fig. 4, accuracy, sensitivity, specificity, precision, and F-score for each class are also displayed. These results reached a classification accuracy of 96% for moderate and high pain and 97% for low pain, improving the results shown in [11], where researchers reported an accuracy between 87% and 90% per class to predict central NP after spinal cord injury.

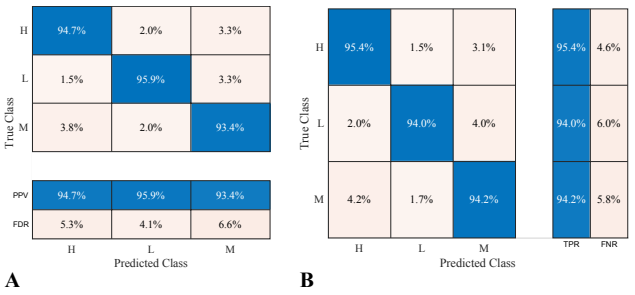

Figure 3. Positive predicted values (PPV) and false discovery rates (FDR) of the SVM confusion matrix. (B) True positive rates (TPR) and false negative rates (FNR) of the SVM confusion matrix.

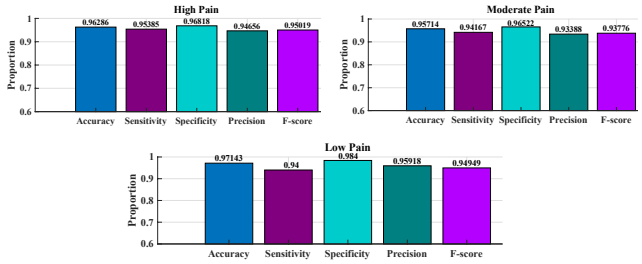

Figure 4. Classifier scores for each level of NP severity. Moderate and high pain reached 96% accuracy and 97% specificity. Low pain reached 97% accuracy and 98% specificity.

D. Statistical Comparison

The fusion of linear and non-linear features to characterize the level of NP severity showed to be significantly different, having applied the one-way ANOVA test ($p<2e-16$) and the Tuckey test for every pair of groups ($p< 0.001$). In particular, the distribution of the most differentiable non-linear feature among the three classes (ApEn at Fz electrode within the BW (0.1~100 Hz)) is presented in Fig. 5. As can been seen, the three levels of NP severity show distinguishable distribution.

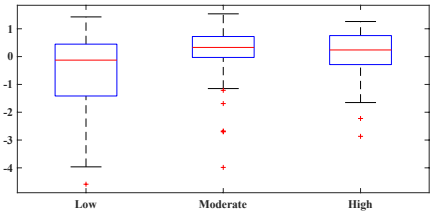

Figure 5. Distribution of the most differentiable non-linear feature coming from Fz electrode within the BW. Y-axis represents the feature values in this electrode and frequency band normalized in the z-score scale.

IV. Conclusion

The aim of the present work was to investigate whether the level of NP severity could be differentiable by patients' report (BIP) along with the analysis of linear and non-linear EEG features (absolute band power and ApEn). By using a SVM classifier, a classification accuracy of 96% was reached, improving the accuracy reported in [11]. Our results show that ApEn is an attribute that effectively characterizes the different levels of chronic NP. For future work, the generalization of the method is desired. For that purpose, a larger sample is necessary, including both genders, a wider range of ages, and diverse clinical histories. The limitations of the study include:

(1) the relatively small sample size, (2) the fact that other cognitive processes are occurring in the brain besides NP, and (3) even with cross-validation, there is a possibility of overfitting from the SVM whenever exposed to unseen data. Thus, this model needs to be tested with new patient data to assure that there is no overfitting. To improve the proposed classifier other methods for feature reduction in the preprocessing stage could be implemented, such as: removing features with near-zero variance or removing significantly correlated features.

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