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Focal epileptic seizures anticipation based on patterns of heart rate variability parameters

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Abstract

Background and Objective: Heart rate variability parameters are studied by the research community as potential valuable indices for seizure detection and anticipation. This paper investigates heart activity abnormalities during focal epileptic seizures in childhood.

Methods: Seizures affect both the sympathetic and parasympathetic system which is expressed as abnormal patterns of heart rate variability (HRV) parameters. In the present study, a clinical dataset containing 42 focal seizures in long-term electrocardiographic (ECG) recordings from drug-resistant pediatric epileptic patients (with age 8.2±4.3 years) was analyzed.

Results: Results indicate that the time domain HRV parameters (heart rate, SDNN, standard deviation of heart rate, upper envelope) and spectral HRV parameters (LF/HF, normalized HF, normalized LF, total power) are significantly affected during ictal periods. The HRV features were ranked in terms of their relevance and efficacy to discriminate non-ictal/ictal periods and the top-ranked features were selected using the minimum Redundancy Maximum Relevance algorithm for further analysis. Then, a personalized anticipation algorithm based on multiple regression was introduced providing an “epileptic index” of imminent seizures. The performance of the system resulted in anticipation accuracy of 77.1% and an anticipation time of 21.8 sec.

Conclusions: The results of this analysis could permit the anticipation of focal seizures only using electrocardiographic signals and the implementation of seizure anticipation strategies for a range of real-life clinical applications.

Keywords: seizure anticipation, heart rate variability, HRV, ECG, seizure prediction, focal epilepsy

1. Introduction

Epilepsy is a chronic neurological disorder that affects about 50 million people worldwide [1]. In 2017, it is estimated that the prevalence and incidence of epilepsy are 6.38 and 0.67 per 1000 persons respectively [2]. Epilepsy is mainly treated with anti-epileptic drugs (AED). Approximately 65-70\% of all cases can be controlled by medication, although only 15\% of these achieve full seizure control without any side effects [3]. Moreover, 7-8\% can be treated by surgical operation. For the remaining 25-30\% of cases, the involved patients suffer from drug-resistant seizures, which cannot be controlled by any of the available treatments. For these cases, reliable seizure anticipation and prediction is of great significance for the patient’s quality of life.

The terms anticipation and prediction are used interchangeably in the literature [4]. A recent review [5], extensively surveys seizure prediction methods with prediction time varying from 5 sec to 90 min. In the present analysis, anticipation is considered as a short-term prediction with an uncertainty of the exact onset time [4].

EEG is by far the most widely adopted clinical technique for the diagnosis, detection, and anticipation and prediction of seizures in clinical practice [4-9]. Although EEG is relative non-invasive and accurate, it is not always convenient for daily monitoring through wearable low-cost devices. Thus, alternative techniques for seizure anticipation and prediction are investigated. It is known that the anterior cingulate, insular, posterior orbitofrontal, and the prefrontal cortices play a significant role in the autonomic nervous system at the cortical level along with the amygdala and hypothalamus [10]. Epileptic seizures are caused due to dysregulations of the sympathetic (SNS) and parasympathetic nervous system (PNS), so heart activity which is also modulated by the autonomic nervous system (ANS) may provide an indicator of the ictal onset. Standardized HRV parameters (described in Table 1) are reliable markers for estimating various aspects of heart activity.

There are several studies investigating the long-term effects of epilepsy on heart activity and the influence of antiepileptic medication [11]. Heart activity is considered a significant factor in epilepsy as specific cardiac patterns relate to underlying mechanisms leading to Sudden Unexpected Death in Epilepsy (SUDEP), a major cause of death in epileptic patients, especially in the case of intractable epilepsy [12]. Epileptic patients present HRV changes such as increased sympathetic and decreased parasympathetic activity, e.g. increased SDNN [13], increased LF, LF/HF 24-36 hours after seizure attack [13] and reduced HF [11, 13] in comparison to controls.

In addition, autonomic alterations expressed in ECG abnormalities, such as ST elevation, sinus arrhythmia, ictal tachycardias, atrioventricular (AV) block and asystole, others, occur during ictal periods [14-16]. ECG itself can also provide useful information in distinguishing episodes of asystolia from epileptic fits leading to clinical episodes originated from ictal arrhythmias [17].

Recently, there is increasing interest in investigating short-term heart activity patterns which are directly associated with
seizures [18], just before (pre-ictal) or during seizures occurrence (ictal) serving for seizure anticipation and prediction. Heart rate (HR), the most straightforward and widely analyzed feature, has been reported to increase during or before seizures in the majority of studies [14, 15, 19-25]. In some cases, studies exploit heart rate increase (HRI) in the pre-ictal phase [26, 27] or nonlinear dynamics such as SD2/SD1 of Poincare plot [27]. The timing of these changes may provide useful clinical information and an additional clinical sign in determining seizures onset. In [21], Cooman proposes an automated online patient-independent seizure detection system based on differential measures related to HRI.

Most of the relevant studies either use ECG as complementary information to EEG [25, 28], or they investigate long-term HRV changes in epilepsy (i.e. without the presence of seizures) [11]. Other studies, use limited HRV parameters (e.g. only the HR or SDNN) [14, 20, 26] not assessing their significance/involvement or not in providing information about each HRV parameter pattern in pre-ictal/ictal phase [14] in order for someone to deploy this knowledge in a seizure anticipation model. There are few studies addressing the problem of seizure anticipation through only HRV analysis [20, 27, 29] and the mechanisms of HRV alterations remain limited [26]. This paper investigates heart activity abnormalities manifested in the HRV parameters and provides a comprehensive analysis of their patterns during pre-ictal and ictal phases as well as the corresponding transition from one phase to the other. In addition, it evaluates and ranks HRV parameters in terms of their relevance, significance and involvement in seizure anticipation and potentially prediction efficacy. The proposed methodology provides a framework for selecting the most important HRV features, incorporating personalized reference information and developing a focal seizure anticipation model only using ECG signals which is an important issue in epilepsy research.

2. Methods

2.1. ECG preprocessing

ECG signal was acquired by placing two Ag/AgCl electrodes in symmetric position of the chest. A typical preprocessed ECG signal acquired during this study is presented in Fig. 1. The signal was detrended and bandpass filtered in order to remove power line noise. Spikes and artifacts (due to the subject’s activity like eye blinks, spikes, head movements, chewing, general discharges) were suppressed by applying dynamic threshold based on neighbourhood envelope.

The R component was extracted using a custom implemented peak detection algorithm based on the signal’s derivative. Firstly, the signal’s derivative was calculated and smoothed. The derivative’s positive peaks were detected corresponding to ECG local maxima and were aligned to the time series using the minimum distance of detected peaks.

![Fig. 1. An example of preprocessed ECG signal from this study, R peaks (red markers) and RR interval determination.](image)

Then, the RR Intervals (RRI) were calculated. The ectopic heartbeats were detected and excluded. Ectopic heartbeats (or cardiac ectopy) are irregular heartbeats that are deviated from normal. There are various ectopic detection methods discussed in detail in [30]. In this study, by adopting the HRV signal approach [30], a heartbeat is determined as ectopic if there is a percentage change of 40% over the averaged previous $n_{elec} = 5$ heartbeats.

$$x_{elec}(t) > 1.4 \cdot \frac{1}{n_{elec}} \sum_{k=1}^{n_{elec}} x(t-k), x_{elec}(t) < 0.6 \cdot \frac{1}{n_{elec}} \sum_{k=1}^{n_{elec}} x(t-k)$$ (1)

An example of ectopic heartbeats detection is presented in Fig. 3. The RR intervals time series were interpolated to a frequency of $f_{samp} = 4Hz$ and detrended by subtracting time series polynomial fit.

2.2. HRV parameters extraction

After the RRI extraction, temporal and spectral HRV parameters were calculated. Temporal HRV parameters were directly computed from RRI according to [31] which is the gold standard for cardiology. The spectral HRV parameters were estimated from the time-frequency representation of the RRI time series [31, 32].

![Fig. 2. Time-frequency representation of RR intervals which is used for the estimation of spectral HRV parameters. The vertical white dashed lines denote the onset and end of the seizure.](image)
The time-frequency representation was estimated using a time-varying autoregressive model [33]. The signal $x(t)$ can be expressed as

$$x(t) = \sum_{k=1}^{p} a_k(t)x(t-k)+e(t) \quad (2)$$

where $a_k(t)$ are the time-varying autoregressive (TVAR) coefficients, $p$ is the model order, and $e(t)$ is Gaussian noise with zero mean and variance $\sigma_r^2$. The model order was selected using the Akaike criterion (AIC) [34] and determined at order 18 leading to normalized spectral indices [35]. The temporal update and evolution of (AR) coefficients were estimated using a Kalman filter algorithm [32] which is an optimal estimator in the mean-square sense. The adaptive time-varying estimation of spectrum achieves enhanced spectral resolution compared to FFT-based spectrum [32], thus enabling reliable estimates even for shorter time periods. The produced spectrogram $S(t,f)$ is discretized into resels (resolution elements) integrating the time interval of each overlapping moving window $\Delta t$ [36]. The energy at each time interval $t_k$, $k=1,2,...,te$ (if: time epochs) can be calculated by the equation

$$S_{resel}(t_k,f) = \int_{t_k}^{(k+1)\Delta t} S(t,f)dt \quad (3)$$

The HRV parameters that investigated in this study divided into time and frequency domain are presented in Table 1. All of them form the feature matrix $X \in \Re^2$ with dimensions $N\times M$ representing $N$ samples and $M$ features (e.g. a specific sample is provided as an $M$-dimensional vector $X(t_i)=[f_1(t_i), f_2(t_i),...,f_M(t_i)]$ and $Y \in \Re$ is the class vector (class 1: non-ictal state, class 2: ictal state).

2.3. Baseline removal and pairwise transformation

For each participant of the experiment, it was considered appropriate to determine a reference period which was carefully selected as an interictal (seizure free) period far from seizures onset. This period corresponds to each subject’s baseline which is removed from all subsequent feature analyses. This transformation generates a common reference to each feature across subjects providing data normalization.

The problem of seizure anticipation can be viewed as a ranking problem where the input is the feature matrix $X$ and the class vector $Y$ described in Section 2.2. In order to transform into a 2-class (classes: ictal, no ictal) classification problem, the pairwise transformation was used as introduced in [37]

$$T: \quad X' = X(t_i) - X(t_j)$$
$$Y' = sign(Y(t_i) - Y(t_j))$$

(4)

where $i,j$ refer to the temporal indices of non-ictal and ictal period respectively with all possible pairs of a specific case of the feature matrix. The transformation procedure is described in Algorithm 1

<table>
<thead>
<tr>
<th>Feature</th>
<th>Unit</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>msec</td>
<td>The mean of RR intervals</td>
</tr>
<tr>
<td>SDNN (or SDRR)</td>
<td>msec</td>
<td>The standard deviation (sd) of RR intervals</td>
</tr>
<tr>
<td>HR</td>
<td>beats/min</td>
<td>The mean heart rate</td>
</tr>
<tr>
<td>STD HR</td>
<td>beats/min</td>
<td>Standard deviation of instantaneous heart rate values</td>
</tr>
<tr>
<td>RMSSD</td>
<td>msec</td>
<td>Square root of the mean squared differences of successive RR intervals</td>
</tr>
<tr>
<td>NN50</td>
<td>count</td>
<td>Number of successive RR interval pairs that differ more than 50 ms</td>
</tr>
<tr>
<td>RR/HR</td>
<td>%</td>
<td>NN50 divided by the total number of RR intervals</td>
</tr>
<tr>
<td>HRV triangular index</td>
<td>–</td>
<td>The integral of the RR interval histogram divided by the height of the histogram</td>
</tr>
<tr>
<td>TINN</td>
<td>msec</td>
<td>Baseline width of the RR interval histogram</td>
</tr>
<tr>
<td>ECG envelope</td>
<td>msec</td>
<td>ECG timeseries envelope</td>
</tr>
</tbody>
</table>

**Algorithm 1 Pairwise transformation used in this study**

Input: $X$ - feature matrix [time x features]  
$Y$ - classes [1: non-ictal, 2: ictal]  
Output: $X'$ - pairwise transformed feature matrix  
$Y'$ - classes [-1,1]  
for each extracted data do  
$X_i, X_j$: feature vectors of class $Y_i,Y_j$ respectively  
Find indices $i,j$ of all permutations without repetition of $X_i,X_j$  
for each pair $(i,j)$ do  
$X' = X_i(t_j) - X_j(t_j)$  
if $Y(t_i)>Y(t_j)$ then $Y'=1$  
if $Y(t_i)<Y(t_j)$ then $Y'=-1$  
end  
end

The pairwise transformation creates preference pairs of feature vectors $X(t_i)\succ X(t_j)=[f_1(t_i)-f_1(t_j),...,f_M(t_i)-f_M(t_j)]$ and their labels $sign(Y(t_i))-Y(t_j)$. If $Y(t_i)>Y(t_j)$ then $X(t_i)\succ X(t_j)$ and this preference pair is a positive instance, otherwise, it is a negative instance $(X(t_i)\prec X(t_j))$. As the dataset of seizure

| Table 1: HRV parameters used in this study |
Fig. 4. Architecture of the ECG seizure anticipation system comprising of 5 subsystems: (a) preprocessing, (b) HRV feature extraction, (c) normalization, (d) feature selection, (e) machine learning.

detection is highly non-balanced, i.e. data from ictal periods are much fewer than non-ictal periods, a balanced dataset should be ensured for formulating a proper model and increasing its performance. Thus, equal samples from both ictal and non-ictal periods were selected for the transformation. The preference pairs and their corresponding labels after transformation can be considered as instances and labels in a new classification problem which then can be performed with traditional classification schemes. In this case, a classifier is trained in order to rank pairs of feature sets with different methods (such as Ranking SVM [37], RankBoost, IR SVM, etc.) for classifying pairwise differences minimizing the misclassification error.

2.4. Important HRV parameters selection

The most relevant and important HRV features are investigated and selected in order to improve the performance of seizure anticipation. The ranking of feature importance was performed using the minimum Redundancy Maximum Relevance (mRMR) selection algorithm [38]. This algorithm evaluates the features’ importance ranking based on maximal relevance and minimum redundancy optimizing in terms of the Mutual Information Quotient (MIQ) criterion [39]. The number of retained features was determined by minimizing the misclassification error using 10-fold SVM discrimination accuracy between ictal and pre-ictal periods.

2.5. Seizure anticipation

The seizure anticipation procedure proposed in this study begins with the ECG preprocessing (Section 2.1), HRV parameters extraction (Section 2.2), baseline removal and pairwise transformation (Section 2.3), HRV features selection (Section 2.4). The architecture of the whole procedure is presented in Fig. 4.

The pairwise transformation of the feature matrix with the selected retained features was used for the regression analysis. A partial least-squares regression model [40] was fitted to the feature matrix $X_{sel}$ with the retained features estimating the involvement of each feature in the regressive response outcome $Y_{reg}$

$$Y_{reg} = \beta_0 + X_{sel} \cdot B^T + e \quad (5)$$

where $\beta_0$ is the intercept, $B=[\beta_1 \beta_2 ... \beta_M]$ are the $M$-dimensional model coefficients of features matrix $X$ and $e$ is the residual (unexplained variance in $Y_{reg}$). The regressive response outcome $Y_{reg}=[y_1 \ y_2 ... \ y_N]^T$ contains the combined information of all selected features being representative of their variation during ictal and no-ictal periods.

The regressive response $Y_{reg}$ is a timeseries (see Fig. 7) which represents an “epileptic index” based on heart activity which increases with an imminent seizure. Thus, significant changes in this index may be indicative of an upcoming seizure. In order to assess the amount of change needed for seizure anticipation, a personalized threshold $thr$ was determined using the equation $thr = \mu + k\sigma$ where $\mu, \sigma$ are the mean and std values $Y_{reg}$ of each participant during interictal baseline. The personalized threshold is a crucial issue as there are different heart activity patterns for each participant as well as different heart activity patterns for each seizure type. The coefficient $k$ provides the confidence interval above the mean interictal $Y_{reg}$ and it was determined as $k = 4.36$ so as to correspond to a $p$-value of 0.05 according to the Chebyshev’s inequality

$$P(|Y_{reg} - \mu| \geq k\sigma) \leq \frac{1}{k^2} \quad (6)$$

A seizure is anticipated by the system after elaborative testing when the regressive response is above the threshold continuously for 5 seconds. When this criterion is fulfilled, the anticipation algorithm will alarm for a seizure detection. The time interval between the moment that an alarm is produced by the anticipation algorithm and the time that the real seizure onset is what we refer to as the anticipation time.

3. Clinical Protocol and procedures

3.1. Inclusion criteria and ethics

Subjects participating in this study are patients diagnosed with non-idiopathic focal epilepsy. If a sustained seizure freedom is not ensured, then even the occurrence of at least one seizure event makes the subject eligible for inclusion in the study. There were some cases for which long-term video EEG and synchronous ECG were recorded, but when evaluated by the two neuropsychiatrists (see Section 3.2), they did not present any epileptic seizure. These cases were excluded from our analysis. The study’s protocol has been approved by the appropriate scientific board of the University Hospital of Heraklion under the reference number 5631/15-5-14. Informed consent was obtained from all patients following a detailed explanation of the study objectives and protocol to each patient and/or caregiver. All caregivers/patients provided written informed consent prior to being monitored.

3.2. Procedure

A patient that meets the criteria described in Section 3.1, as evaluated by an expert neuropediatrician, was admitted to
the hospital. Her/his medical health record was created including clinical data about demographics, medical history, family history, medication, epilepsy classification, etc. An EEG cap with 10/20 electrode system was placed in the head of the patient, a camera was placed opposite the patient’s bed and additional sensors for recording the breath rate and SpO2 were utilized. For the ECG recording, the patient’s skin was prepared using prepping gel and conductive paste. Two Ag/AgCl electrodes were placed in symmetric position of the chest corresponding to the leads V1 and V2 which they are considered as the most appropriate in order to acquire bipolar ECG recording [44]. Long-term video, EEG and ECG signals were recorded simultaneously for each patient during hospital monitoring for about 12-24 hours. The long-term EEG recordings were independently evaluated and annotated for epileptic seizures and pathological findings by two expert neuropediatricians.

3.3. Dataset

The clinical dataset has been recorded at the University Hospital of Heraklion and contained 9 participants (3 females, 6 males). Their age was 8.2±4.3 years at the moment of monitoring. The recorded dataset included 42 seizures in total. The seizures classification into standardized types and subtypes was performed according to the criteria of the International League Against Epilepsy (ILAE) [41]. Table 2 presents patients demographic data as well as selected clinical data. It should be noted that the dataset contains only cases of focal seizures in order to share similar clinical characteristics. Four additional cases were excluded from the study due to excessive body motion induced artifacts in the ECG or other errors, such as the removal of an electrode from the chest.

Besides, a significant aspect is the determination of the recordings segments should be involved in the analysis. Various studies mention that according to the seizure type, the post-ictal period may be long-lasting (in some cases from 10-30min up to 5-6 hours) [18, 42] with HRV measures having a behaviour similar to the corresponding ictal phase. In this study, this phenomenon was checked eliminating post-ictal periods which retain HRV statistical properties in relation to the corresponding ictal period. In addition, the sleep periods of interictal periods were identified and eliminated as HRV parameters are affected by sleep stage transition and micro-arousal [29, 43, 44]. Finally, there were periods such as removing the EEG device in order the participant to go to the bathroom, eating meals, periods with extreme body motion and periods where the participants (children) touched/removed the electrodes which were identified through video recordings and eliminated from the analysis. The baseline period was selected carefully as an interictal period (seizure-free condition) away from seizures existence. Thus, the dataset finally selected for the analysis of this study followed the aforementioned rules in order to eliminate non proper segments and to determine the pre-ictal, ictal and postictal period respectively. According to this, the recording minutes analyzed for each participant are presented in Table 2.

4. Results

The methodology for seizure anticipation was applied to the clinical dataset of this study. The HRV parameters were estimated from the ECG recordings using the methods described in Section 2.2. The sampling frequency of the ECG signal is $f_s=256Hz$ and a sliding temporal window of $\Delta t=30sec$ and step 2sec was used. The time window interval was chosen in order to be able to track HRV temporal dynamics, while it was checked that the increase of time window does not affect significantly system performance, as also referred in relevant studies [45].

Specific HRV parameters presented abnormal patterns during seizure occurrence. The most prominent feature

![Fig. 5. Mean time series across all seizures presenting the evolution of the HRV parameters HR, LF/HF, signal upper envelope, LF$_{norm}$ SDNN and HF$_{norm}$. Seizure onset occurs at t=0 and the vertical dashed lines denote the onset/ending and the red area the seizure area.](image_url)
Table 3: Summary statistics of the HRV parameters during reference and ictal periods

<table>
<thead>
<tr>
<th>Feature</th>
<th>Mean control</th>
<th>Mean ictal</th>
<th>p-value</th>
<th>sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>0.69</td>
<td>0.58</td>
<td>0.000</td>
<td>↓</td>
</tr>
<tr>
<td>SDNN</td>
<td>0.063</td>
<td>0.080</td>
<td>0.001</td>
<td>↑</td>
</tr>
<tr>
<td>HR</td>
<td>91.6</td>
<td>108.1</td>
<td>0.000</td>
<td>↑</td>
</tr>
<tr>
<td>HR$_{\text{std}}$</td>
<td>8.15</td>
<td>13.36</td>
<td>0.000</td>
<td>↑</td>
</tr>
<tr>
<td>RMSSD</td>
<td>0.06</td>
<td>0.06</td>
<td>0.870</td>
<td>ns</td>
</tr>
<tr>
<td>NN50</td>
<td>11.74</td>
<td>10.28</td>
<td>0.092</td>
<td>ns</td>
</tr>
<tr>
<td>pNN50</td>
<td>30.26</td>
<td>23.01</td>
<td>0.001</td>
<td>↓</td>
</tr>
<tr>
<td>HRV$_{\text{rs}}$</td>
<td>8.38</td>
<td>8.58</td>
<td>0.453</td>
<td>ns</td>
</tr>
<tr>
<td>peak_LF</td>
<td>0.10</td>
<td>0.09</td>
<td>0.108</td>
<td>ns</td>
</tr>
<tr>
<td>peak_HF</td>
<td>0.21</td>
<td>0.21</td>
<td>0.602</td>
<td>ns</td>
</tr>
<tr>
<td>total power</td>
<td>3.80E+05</td>
<td>4.86E+05</td>
<td>0.000</td>
<td>↑</td>
</tr>
<tr>
<td>LF</td>
<td>1.76E+05</td>
<td>2.58E+05</td>
<td>0.000</td>
<td>↑</td>
</tr>
<tr>
<td>HF</td>
<td>1.64E+05</td>
<td>1.51E+05</td>
<td>0.229</td>
<td>ns</td>
</tr>
<tr>
<td>LF$_{\text{norm}}$</td>
<td>0.45</td>
<td>0.52</td>
<td>0.000</td>
<td>↑</td>
</tr>
<tr>
<td>HF$_{\text{norm}}$</td>
<td>0.45</td>
<td>0.34</td>
<td>0.000</td>
<td>↓</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.40</td>
<td>2.14</td>
<td>0.000</td>
<td>↑</td>
</tr>
<tr>
<td>upper envelope</td>
<td>335.0</td>
<td>386.4</td>
<td>0.003</td>
<td>↑</td>
</tr>
</tbody>
</table>

$\uparrow$: significant increase; $\downarrow$: decrease during seizure in relation to interictal period, ns: non-significant difference

Table 4: Classifiers Performances of Discrimination Accuracy for the Selected HRV Features (left panel), Classification plot and decision boundaries of the SVM (which achieves best classification accuracy) for the 2 top-ranked features for visualization purposes (blue: non-ictal, red: ictal) (right panel)

<table>
<thead>
<tr>
<th>Classifiers</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KNN</td>
<td>98.36</td>
</tr>
<tr>
<td>GLM</td>
<td>94.57</td>
</tr>
<tr>
<td>NVB</td>
<td>84.32</td>
</tr>
<tr>
<td>LDA</td>
<td>89.94</td>
</tr>
<tr>
<td>SVM</td>
<td>99.63</td>
</tr>
<tr>
<td>RF</td>
<td>98.49</td>
</tr>
</tbody>
</table>
KNN, Generalized Linear Model (GLM), Naïve Bayes (NBV), Linear Discriminant Analysis (LDA), Support Vector Machines (SVM), Random Forest (RF) classifiers. The results are shown in the left panel of Table 4 where SVM outperform all other classification schemes with a classification accuracy of 99.63%. A classification plot with the decision boundaries of the SVM for the 2 top-ranked features along with samples of a testing fold (blue: non-ictal, red: ictal) is presented in the right panel of Table 4 presenting the data separability achieved and the discrimination efficiency of the proposed methodology.

Then, the system’s performance is investigated on seizure basis which is closer to what a system or a seizure device is summoned to perform. A regression model fitted the data, as described in Section 2.5, leading to the formulation of regression response $Y_{reg} = f_{reg}(X_{in})$ as a linear combination of predictors (transformed HRV parameters). This response can be considered as an "epileptic index" which increases with the imminent occurrence of a seizure. A typical pattern of regression response is presented in Fig. 7, where the response increases and exceeds the threshold (horizontal dashed line) indicating the existence of an upcoming seizure.

The seizure anticipation was performed using the model described in Section 2.5 where the threshold is determined in a personalized basis for each subject sampling a 5min period from the interictal state (where heart activity could be considered as control reference). The performance of seizure anticipation was investigated in terms of classification accuracy and anticipation time. A 10-fold cross-validation process was performed on seizure basis resulting in a mean accuracy of 77.1% and an anticipation time of 21.8 sec.

5. Discussion
This study proposes a system for seizure anticipation based on HRV parameters on focal seizures in childhood. The results indicate significant cardiac autonomic alterations during seizures. Specifically, the HRV features HR, SDNN, HRstd, total power, LF/HF, LF, LFnorm. ECG upper envelope significantly increase and the features RR, HRnorm, pNN50 significantly decrease making them efficient features for seizure anticipation. The features were ranked in terms of their significance and relevance to seizure anticipation leading to the selection of the 11 top-ranked features (HR, LFnorm, upper envelope, HFnorm, HRstd, LF, total power, SDNN, LF/HF, pNN50 and HF).

The proposed seizure anticipator was evaluated on clinical ECG recordings dataset contained 42 seizures coming from 9 subjects being in line with other published studies which evaluated their methods using datasets of 3 patients [28], 22 seizures [29], 47 seizures [20]. Despite the fact that a bigger sample would enhance the generalizability of the results, the number of seizures of this dataset is sufficient for parametric analysis with a confidence level of 95%, and power 95% based on power calculations described in [46].

The performance of the seizure anticipation algorithm employed in the present study utilizing HRV parameters is 77.1% anticipation accuracy with mean anticipation time of 21.8 sec. Even though literature is limited but with increasing interest [18] and research groups use different datasets so as direct comparative evaluation not to be possible, this study achieves similar results in relation to relevant studies using only ECG which refer corresponding anticipation accuracies of 84.72% [47], 86.1% [27], 83.87% [21], 70.45% [45]. All these studies have been conducted to adults in contrast to our study which conducted to children where it is known that HRV is increased and unstable. In fact, it is more difficult to anticipate seizure through HRV in smaller age children which is also supported by the present study. It is characteristic that, in our study, difficulties in seizure anticipation are concentrated in 2 specific children of 4 and 5 years old and specific segments containing 3 seizures without them the accuracy percentage would be 83%.

It should be noted that ECG performance is, as expected, inferior to using EEG signals in terms of predictive evidence, localization ability, and temporal resolution. However, the interest of the scientific community on the usage of only one ECG channel makes these methods appropriate, as they can be conveniently used through wearable devices in daily monitoring.

A crucial issue is that the HRV parameters can be also affected by various conditions not related to an epileptic seizure. These conditions may originate from various reasons such as physical activity (e.g. walking, running, stair climbing), body motion, emotional status, arousal and micro-arousal phases, medication, etc. To our knowledge, there are no consistent studies discriminating the activations of the SNS and their corresponding effects on heart activity caused by conditions with and without ictal origin. Aforementioned users’ activities should be avoided as they may mislead and deteriorate the system’s anticipatory performance. In this study, some of these conditions were identified and annotated as video-EEG was recorded simultaneously with ECG, and periods corresponding to seizures (EEG annotations) and periods corresponding to aforementioned states were identified through video recordings and eliminated from the analysis.

Regarding the practical applicability of the proposed method, it should be noted that this study took place in a hospital environment, i.e. real settings but in a more controlled environment in relation to a home environment. The most significant issue is the long-term validation of the proposed method which was not possible in this study, the participants were monitored for a few hours until one or more seizures were recorded following the clinical protocol of the hospital and then they were leaving the hospital following the medication proposed by the clinician doctors. A research pilot should be established in the future in order to investigate
system’s behaviour for a long term period and the applicability in a more convenient device (e.g. patch, watch, vest) than electrodes placed in the chest as in this study.

Further studies and increased sample size would increase the model’s reliability, accuracy as well as to estimate the importance of the involved HRV parameters. Even though cardiac signals contain limited information, this study indicates that the usage of ECG recordings only could serve efficiently seizure anticipation while they can be conveniently recorded through handy wearable devices.

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Ethical approval statement

This study’s protocol was approved by the appropriate scientific board of the University Hospital of Heraklion under the reference number 5631/15-5-14. Informed consent was obtained from all patients following a detailed explanation of the study objectives and protocol to each patient and/or caregiver. All caregivers/patients provided written informed consent prior to being monitored.

Conflict of interest statement

The authors declare no conflict of interest.

Funding and Competing Interests

All authors declare none.

References


