The power of ECG in multimodal seizure monitoring: visual recognition and added value to an EEG-based detector using limited channels

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Summary

Objective: Focal seizures have localizing ictal full-scalp EEG changes in around 20% of focal aware and 50-70% of focal impaired awareness seizures. Ictal tachycardia was observed in 71 - 84% of the seizures, most commonly from temporal lobe origin. We aim to develop a semi-automatic seizure detection algorithm to detect focal seizures in an outpatient setting. First, the algorithm will reduce the vast amount of recorded data. Second, the neurologist has to review the automatically flagged regions and decide whether it was a seizure or a false positive. In this framework, we determined the sensitivity of behind-the-ear EEG and ECG in the detection of focal seizures, and quantified the added value of ECG to EEG. In the development of a wearable seizure detection device based on behind-the-ear EEG, we have reported that a neurologist using only the behind-the-ear EEG channels could recognize 62% of seizures with ictal EEG changes on full scalp EEG. In the present study, we determined whether blinded visual recognition of ictal tachycardia/bradycardia was possible.

Methods: This study analyzed three multicenter databases consisting of 129 patients having focal epilepsy and a total of 851 seizures. A multimodal automated seizure detection algorithm was developed using behind-the-ear/temporal EEG and single-lead ECG electrodes. The results were shown as 'sensitivity in function of false alarm rate' graphs. Two readers were asked to annotate ECG segments containing selected seizure or non-seizure fragments.

Results: The multimodal algorithm outperformed the EEG-based algorithm in two of three databases with an increase of 10% and 8% in sensitivity for the same false alarm rate. The visual ictal ECG recognition study resulted in an averaged sensitivity of 79% with a specificity of 87.5% for the two readers.

Significance: ECG can be of added value to an EEG-based seizure detection algorithm using only behind-the-ear or temporal lobe electrodes for patients with focal epilepsy. Visual recognition of ictal tachycardia/bradycardia is possible.

Key Points

- ECG can be of added value to an EEG-based seizure detection algorithm using only behind-the-ear or temporal lobe electrodes for patients with focal epilepsy.
- Visual recognition of ictal ECG patterns is possible in a selected number of patients.

Introduction

Epilepsy is amongst the most common neurological disorders, affecting almost 1% of the population worldwide[1]. Anti-epileptic drugs provide adequate treatment for about 70% of patients[2]. The remaining 30% continue to have seizures, which drastically affect their quality of life. To optimize therapeutic interventions for these patients, objective measures of seizure documentation and counting are needed[3]. However, seizure self-reporting by patients is

unreliable[4,5,6,7,8]. Wearable seizure detection devices could provide a more reliable seizure documentation. In the SeizeIT1 project, we studied the possibility to record behind-the-ear EEG. Consequently, algorithms were developed using only behind-the-ear EEG channels for patients with focal epilepsy[9,10]. Sensitivity of full-scalp EEG to localize focal seizures has been reported to be around 21% in focal aware[11] and 50-70% in focal impaired awareness seizures[12,13,14]. Furthermore, from the seizures with EEG correlation on full scalp EEG, 62% could be annotated as a seizure by a neurologist using only the behind-the-ear EEG channels[10].

Ictal heart rate changes as measured with electrocardiography (ECG) have been shown useful for seizure detection in patients with focal epilepsy[15,16,17,18], especially temporal lobe epilepsy. Ictal tachycardia was observed in 71 - 84% of the seizures[19,20,21]. Multimodal algorithms were developed[22,23,24], but the question whether the inclusion of ECG increases the performance of an EEG-based seizure detection remains unanswered. Visual recognition of ictal tachycardia remains uninvestigated, useful when the neurologist will visually assess the automated seizure detections. Figure 1 shows the behind-the-ear EEG and ECG signals during a seizure.
In this paper, a multicenter database, consisting of 129 patients with focal epilepsy and 851 seizures, was analyzed for the development of an automated multimodal seizure detection algorithm using three channels EEG and single-lead ECG. The added value of ECG in comparison with EEG-based seizure detection was investigated. For those patients having an adequate performance using ECG only, a visual analysis was performed. We studied whether it is possible to detect seizures visually based only on ECG.

This is a class 1 study according to the standards for testing seizure detection devices[25], because real seizure data from patients were included and gold standard annotations were used for validation. However, the data were not acquired with wearables.

Methods

1. Data acquisition

The data used in this study consists of 3 different databases: SeizeIT1, Epilepsiae Freiburg and Epilepsiae-Paris. Since variability in performances across datasets is high, including multiple datasets is important in order to derive general claims.

A. The SeizeIT1 dataset

The SeizeIT1 dataset contained recordings from 82 patients with refractory focal epilepsy, who underwent presurgical evaluation at UZ Leuven, Belgium. Only those patients having at least two focal epileptic seizures with ictal EEG changes and a length of at least 10 seconds were used in this study. These inclusion criteria were set to allow training and testing of a personalized algorithm. The dataset consisted of 36 patients having in total 176 seizures. Most seizures were focal impaired awareness (FIA) seizures, originating from the temporal lobe with a length between 30 and 60 seconds. The overview of seizure types, localization, lateralization and seizure duration is given in Figure 2. Patients were recorded using the 10-20 EEG system and one bipolar ECG. Additionally to the standard equipment, four behind-the-ear EEG electrodes (two at each side) were recorded, which were used in this study. From the total of 176 seizures, 109 (62%) could be blindly recognized by a neurologist using only the behind-the-ear EEG channels. More information on the SeizeIT1 dataset is described in detail in Vandecasteele et al.[10].

B. The Epilepsiae-Freiburg and Epilepsiae-Paris datasets

The Epilepsiae-Freiburg and Epilepsiae-Paris datasets are subsets of the surface EEG Epilepsiae Database[26,27], recorded in Freiburg, Germany and Paris, France. The Freiburg dataset consisted of 30 patients having in total 275 seizures, whereas the Paris dataset contained 63 patients having in total 400 seizures. Information about seizure localization/lateralization was provided for these datasets by the electrodes involved during the seizure onset, listed for each seizure. Most of the seizures were FIA seizures originating in the (fronto-) temporal lobe with a duration between 60 and 120 seconds for both datasets. The overview of seizure types, localization, lateralization and duration is provided in Figure 2. In the Freiburg dataset, 243 (88%) seizures had ictal EEG changes, whereas all the seizures from the Paris dataset were associated with ictal EEG changes. From the Freiburg/Paris dataset, 196 (71%)/278 (70%) seizures had temporal lobe involvement. The patients were recorded with 10-20 scalp EEG with one bipolar ECG. No behind-the-ear channels were recorded as in the SeizeIT1 database. In our study, we have used the closest electrodes to the behind-the-ear placements as surrogates: namely, the T7, T8, P7 and P8 electrodes[28].

2. *Automated seizure detection algorithms using EEG and ECG*

    a. *Unimodal EEG-based seizure detection algorithm using only behind-the-ear/temporal EEG electrodes*

A patient-specific algorithm for offline seizure detection[10] was used as unimodal EEG-based seizure detection algorithm. For SeizeIT1, only the behind-the-ear EEG channels were used[10]. For the Epilepsiae databases, those specific EEG channels were not recorded and the mid-posterotemporal electrodes T7, T8, P7, and P8 were used instead.

1) Feature extraction: The data was segmented into 2-second windows with 1-second overlap. For each window in the features were extracted.

2) Classification: In order to classify those 2-second windows, a support vector machine (SVM) with a radial basis function kernel was applied. To train the SVM model for SeizeIT1, original seizure annotations (onset and end of seizure) from the neurologist were adapted by an engineer to exclude artifacts and non-typical EEG patterns[10]. For the Epilepsia datasets, the provided annotations were used to train the models. In order to obtain 'sensitivity in function of false alarm rate (FAR)' graphs, the continuous output of the SVM classifier was rescaled to a probability between 0 (very low probability) and 1 (very high probability to be a seizure segment). By changing the cut-off value for this probability, ROC graphs were obtained with the sensitivity in function of FAR.

3) Cross-validation: A patient-specific seizure detection algorithm was applied in this work, meaning that we used data from the test patient to train the models. The cross-validation scheme was leave-one-seizure-out.

b. Unimodal ECG-based seizure detection algorithm

A new patient-independent ECG algorithm was developed using the SeizeIT1 database. The performance of the algorithm was compared to two state-of-the-art algorithms in appendix A. The different steps of the algorithm are summarized.

1) R-peak detection: The method consists of an ensemble of three different R-peak detection algorithms. The first one is based on a wavelet decomposition[29], the second one extracts the R-peaks from the derivative signal with an adaptive threshold[16] and the last one uses an adapted version of the Pan-Tompkins algorithm. Upper and lower envelopes were extracted to obtain a clean signal[30]. The different R-peak detection algorithms generate three different R-peak series. These R-peak locations were combined with an ensemble method[31].

2) Feature extraction: The data was segmented in windows of 60 seconds with 10 seconds overlap. Compared to EEG (windows of 2 seconds), larger windows are needed to extract reliable

ECG features. For each window 133 features were extracted (the detailed description of all the features is provided in Appendix B). The feature set consisted of different features both from the time domain Heart Rate Variability (HRV), frequency domain HRV and other features also applied in various (non-)epilepsy publications[16,32-40].

3) Feature selection: In order to select discriminatory features, a random-forest based feature selection scheme[41] resulted in a subset of the six most discriminant features, namely: the modified cardiac sympathetic index based on Lorenz plot (CSI100)[32], circadian rhythm-based feature, duration of the Heart Rate (HR) increase, HR after tachycardia/ HR before tachycardia, Very Low Frequency (VLF) power and Low Frequency (LF) power.

4) Classification: In order to classify each 60-second window, a random-forest classifier was used. Following the rationale used in the EEG-algorithm, the continuous output of the random forest was converted to a probability and an ROC 'sensitivity versus FAR' graph was computed.

5) Cross-validation: A patient-independent seizure detection algorithm was developed. The cross-validation scheme was leave-one-patient-out for SeizeIT1. The Epilepsiae databases were tested with a model trained on SeizeIT1.

c. Multimodal seizure detection algorithm

Different strategies to fuse multiple modalities exist; the main categories of such fusing strategies are the early and late fusion. In this work, we opted for a late integration strategy due to the difference in the cross-validation schemes used and the different alignment of the events in both modalities. More specifically, a patient-specific cross-validation scheme led to optimal results for the EEG-based model[10], while for ECG, the lack of available data points per patient did not allow the application of exactly the same patient-specific cross-validation scheme without overfitting the model. In the case of EEG, multiple 2 second windows are available per seizure whereas for

ECG, only one heart rate increase is present per seizure. Secondly, the typical patterns of EEG and ECG do not occur exactly at the same time. The HR increase/decrease can follow or precede the EEG onset[20]. Hence, a late integration, 'OR' strategy, has been applied: a seizure should be detected by at least one of the modalities (EEG or ECG) in order to generate a seizure detection alarm, similarly to Fürbass et al.[22]. This choice was made since not all seizures have ictal ECG changes or EEG correlation and we aimed for a high sensitivity.

For this multimodal algorithm, there are two varying thresholds (one for EEG and one for ECG). If we want to show all possibilities, the results would be a plane to be visualized in 3D. For simplicity, a threshold was selected for each modality leading to 0.2 FP/hour and those two thresholds were used to produce the multimodal results. This procedure was also done for an FAR/hour of 0.5 and 1.

d. Performance evaluation

The following measures were applied to determine the performance of the seizure detection algorithm:

1) Detection sensitivity: TP/ (TP+FN), where TP is a true positive and FN is a false negative. A seizure was detected correctly (TP) if a detection occurred between the EEG onset and offset of the seizure.

2) False alarm rate (FAR) per hour: False Positives (FPs)/recording length. FPs within 10 seconds of each other were counted as one FP. FPs happening 60 seconds before the seizure onset or 60 seconds after the seizure offset were not counted as false alarms since ictal tachycardia can precede EEG seizure onsets.

3) F1-scores and PPV values were not calculated since those metrics will be lower for algorithms aiming at a large sensitivity (with unavoidably a higher FAR).

The ’sensitivity in function of FAR’ graphs were constructed by changing the cut-off values of the probabilities both for the ECG- and EEG-based algorithms. For each patient a graph was constructed, and the graphs of all patients were averaged.

3. Visual seizure recognition using only ECG

ECG segments and the derived HR containing seizures and non-seizures were presented to two blinded readers: one neurologist (JMO) and one Biomedical science PhD student (LS). A preselection of patients was performed for this study. Only the patients with a ‘high performance’ using the ECG-based seizure detection (a sensitivity higher than 75% with an FAR of 1/hour) and patients having at least three seizures were included. This resulted in a dataset of 44 patients (34% of total patients). All the seizures of the included patients were shown to the readers. The non-seizure segments were false detections made by the ECG-based algorithm with a threshold leading to a FAR of 1/hour. Out of those false alarms, 25 false alarms were randomly selected. Since we foresee a personalized approach, the first two seizures of each patient were shown before starting the experiment. In addition to annotating the ECG segment as seizure or non-seizure, the suspected reason for the algorithm having falsely detected the segment (artifact or physiological tachycardia) was also noted.

Since the readers were not used to annotate seizures based on ECG, two trial exercise sessions took place, each having 3 subjects. After annotating the segments of each patient, the performance of their annotation was presented to the readers along with the false positives and false negatives.

The segments were shown using Matlab 2020a. For each segment, two subplots were presented to the readers. The first one contained the filtered ECG with a bandpass filter [1-45Hz], together

with the detected R-peaks. The second one contained the extracted HR in beats per minute. The readers could zoom in and out on those figures. Examples are shown in Figure 3.

To evaluate the performance, sensitivity and specificity were defined as the percentage of recognized and non-recognized seizure and non-seizure segments, respectively. The time each reader used to annotate all the segments was recorded. Furthermore, the correspondence between the two readers was calculated based on a Kappa score[42]. This value is computed as $K = \frac{p0-pc}{1-pc}$ with $p0$ the observed agreement and pc the hypothetical probability of chance agreement. To summarize the performance measures across the dataset, average values, standard deviations and the median with range [minimum and maximum] were calculated.

Results

1. Performance of the Unimodal models: EEG and ECG

In Figure 4 the 'sensitivity in function of FAR' graphs are shown for the unimodal algorithms: EEG and ECG. Table I.A shows the average sensitivities corresponding to a FAR of one FP/hour. For the EEG-based algorithm, Epilepsiae-Freiburg had the lowest sensitivity (77%), Epilepsiae-Paris had a sensitivity of 82%, whereas SeizeIT1 had the highest sensitivity (84%). For the ECG-based algorithm, Epilepsiae-Freiburg had the highest sensitivity (74%), SeizeIT1 had a sensitivity of 68%, whereas Epilepsiae-Paris had the lowest sensitivity (52%). For all the databases, the EEG-based seizure detection algorithm had the highest average and median sensitivities. By analyzing individual patients, 82 patients (64%) exhibited a higher sensitivity with EEG, 31 patients (24%) had equal sensitivity with EEG and ECG and 16 patients (12%) exhibited a higher sensitivity with ECG. In total, 443 seizures (52%) were detected with both EEG and ECG, 233 seizures (28%) were detected only with EEG, and 121 seizures (14%) were not detected either with EEG nor with ECG. It shall be noted that 53 seizures (6%), from 35 patients, were detected

only with ECG. Appendix C describes the percentage of detected seizures in function of seizure type and localization for the different modalities.

2. Performance of the Multimodal model

In Figure 4, we present the results of the multimodal algorithm. The outcome of the two unimodal algorithms were combined with a late integration approach at three discrete thresholds: the thresholds leading to 0.2 FP/hour, 0.5 and 1 for both the EEG and ECG algorithm. Those three (sensitivity, FP/hour)-pairs were shown together with the corresponding sensitivities leading to the same FAR on the EEG graph. By analyzing those three pairs, the lowest increase in sensitivity was observed with the 0.2 FP/hour threshold and the highest with the 1 FP/hour threshold. In Table I.B the sensitivity of the multimodal algorithm (threshold leading to 1 FP/hour) is presented along with the outcome of the EEG-based detectors with the same FP/hour. For SeizeIT1, an increase was observed from 85% (EEG unimodal) to 95% (Multimodal). A similar increase was seen for Epilepsiae-Freiburg (from 82 % to 90%). No increase was observed for Epilepsiae-Paris (from 84% to 84%). In total, 29 (22%) patients had increased sensitivity (with the multimodal algorithm compared to the EEG unimodal), 87 (67%) patients had the same sensitivity and 13 (10%) patients had a decreased sensitivity.

3. Visual seizure annotation using only ECG

In Table II the results for the visual seizure annotation, using only ECG, are shown. In total for all datasets, an average sensitivity of 79% with a specificity of 87.5% was obtained. Assuming the annotators would have similar performances on the remaining non-seizure segments (false alarms detected by the algorithm), the false alarm rate would be in total 3FP/24hour on average. The time needed to annotate one patient (all the seizures with 25 false alarms for each patient) was on average 8.0 minutes for reader 1 and 4.4 minutes for reader 2. The average kappa value was 0.76, which implies a substantial consistency of the two readers in terms of accuracy. The

percentage of false alarms due to artifacts was 42% and 44%, respectively according to the two readers.

Discussion

Mobile health and digital biomarkers involve the application of wearable sensors to obtain data pertinent to wellness and disease diagnosis, prevention and management[43]. Current wearables in epilepsy are accelerometer- and EMG-based devices for online-automated detection of tonic-clonic seizures, mostly for generalized tonic-clonic seizures, the easiest group of seizures to detect. Those wearable devices generate an immediate alarm for caregivers and health care professionals. These devices have a sensitivity of around 90% and a PPV of around 55%. The F1-score of these devices is around 0.68[44,45]. These devices are sold directly from the company to the patient without involvement of the neurologist-epileptologist, which is a B-C (business to client) business model. It is a disadvantage that the neurologist cannot review the raw signals of the seizure detections, making it impossible to determine with hindsight whether a detection represented a seizure or a false-positive detection.

No wearable devices are currently available for the detection of focal seizures. An important methodological problem is the diversity of focal epileptic seizures: there are three focal seizure types, namely focal aware, focal impaired awareness and focal to bilateral tonic clonic seizures, which can be generated from four different lobes, namely temporal, frontal, occipital and parietal lobe[46]. One biosignal will not allow detection of all focal seizures, as we found. Variability in performances across datasets is high, multiple datasets were included in this study to derive general claims. In our study, a multicenter dataset of 129 patients with 851 seizures recorded during a presurgical evaluation was used. Behind-the-ear/temporal EEG plus ECG captured 52% of seizures, EEG-alone 27% and ECG-alone 6%. In those 6%, probable reasons why those

seizures could not be picked up with EEG are listed in appendix D. Around 21% of the seizures remained difficult to detect with behind-the-ear EEG, which was due to unclear ictal EEG patterns, short seizures or artifacts on the restricted set of temporal lobe or behind-the-ear electrodes. These observations suggest that wearables to detect focal seizures should be multimodal, i.e. able to capture different biosignals. The neurologist should be aware of ictal EEG and ECG changes of an individual patient beforehand in order to select the biosignals to capture with the multimodal wearable device. This would also allow creating a personalized algorithm, i.e. trained with seizure data from the individual patient, as in our study. We have shown before that personalized algorithms are more sensitive than patient-independent ones[10,47]. With our current algorithm, 14% of all seizures were not captured with EEG or ECG. The majority of those seizures had an unclear or fronto-temporal onset zone. Seizures with an unclear origin often have motion and noise artifacts on the EEG, which complicates localization. Seizures from the fronto-temporal origin could have an onset zone in the frontal area. Those seizures are typically associated with motor and muscle components and could be picked up with electromyography (EMG). Adding EMG/motion to the analysis could potentially increase the sensitivity even more.

By comparing our results with the literature, Fürbass and colleagues[22] reported a sensitivity of 72% with an FAR of 4.0 FP/24hour (0.17FP/hour) using seven posterior EEG electrodes for focal seizures. Our EEG-based algorithm, using four electrodes behind-the-ear or mid-posterotemporal electrodes achieved an average sensitivity of 73% at 0.2FP/hour. Fürbass and colleagues[22] had a sensitivity of 27% with an FAR of 0.7 FP/24 hour using ECG. Our ECG-based algorithm achieved an averaged sensitivity of 13% for the same FAR. Those results for EEG are

comparable; our results for ECG are slightly lower. However, the EEG electrodes, cross-validation and the dataset are different which undermines the rigor of the comparison.

Our 'sensitivity in function of FAR-graphs' showed that high sensitivity can be obtained at the cost of a higher number of false positive detections. In our view, the FAR is too high to use the algorithm for online/immediate seizure detection in daily practice. It would be very useful, however, to use the algorithm to reduce the vast amount of recorded data. The neurologist has only to review the automatically flagged regions and decide whether it was a seizure or a false positive detection. Our multimodal algorithm had a high average sensitivity of 90% at 2 FP/hour. This would mean that two data points should be reviewed per hour, which would reduce the review time with probably more than 90%. This would make the wearable device a medical device under full supervision of the neurologist, who is in charge of prescribing the device and final interpretation. This represents a B-B-C (business to business to client) business model. We have shown that ictal EEG changes can reliably be detected on behind-the-ear EEG. In addition to ictal EEG changes, which are familiar to neurologists, we showed that the pattern of ictal ECG changes could be used in selected cases in combination with EEG or even in isolation to confirm the presence of a seizure. We obtained an average sensitivity of 79% with a specificity of 88%. In the current study, patients having at least 75% sensitivity with an FAR of 1/hour with the ECG-based algorithm were included. Jepessen and colleagues[17] reported that an ictal HR change of more than 50 beats per minute is a positive predictor of an epileptic seizure. In our study, a large group of patients had no or mild HR increases (20 -30 beats per minute). This made the visual recognition task more difficult and resulted in lower performances. Important properties according to the readers to perform this annotation task was the similarity in HR pattern with the two example ictal ECG segments, the increase in HR (beats per minute) and the duration of the

tachycardia. Visual assessment of ictal HR changes to detect epileptic seizures warrants further study.

When developing a wearable, good quality of signals will be vital to obtain reliable results. In the current study, a lower sensitivity for the ECG-based algorithm was observed for Epilepsiae-Paris. By inspecting the raw ECG data, an increased number of artifacts was observed. Those artifacts looked like motion artifacts with usually high frequency muscle activity on top. In the visual annotation study using ECG, therefore, the number of false alarms due to artifacts was higher in Epilepsiae-Paris (60%) compared with Epilepsiae - Freiburg (37%) and SeizeIT1 (23%).

To integrate the EEG and ECG, a late integration approach with an 'OR' strategy was applied: the ECG or the EEG should give a seizure detection to generate a seizure detection alarm. Other integration strategies should be investigated. Probably, the added value of ECG is the largest when EEG is noisy or when EEG is uncertain whether it is a seizure or not. Based on the level of noise on the raw signals and the certainties of detections (seizure/no seizure), different weights could be assigned to the output seizure probabilities of the two modalities. To quantify uncertainties, trust scores could be a good methodology[48].

The present work was part of the SeizeIT1 project, in which we used EEG and ECG data from standard hospital equipment. We are continuing this work in the SeizeIT2 project https://eithealth.eu/project/seizeit2/ (ClinicalTrials.gov: NCT04284072) with a multimodal wearable based on Byteflies's Sensor-Dot (https://www.byteflies.com/) , measuring two channels EEG behind-the-ear, ECG, accelerometry and EMG of the left deltoid muscle. We are planning to determine F1 scores for typical absences, focal seizures and tonic-clonic seizures in a hospital-

based and home-based international multicenter study. We are further developing new and improved electrode patches to measure EEG, ECG, EMG, respiration, oxygen saturation and skin temperature in the study of epileptic seizures (ClinicalTrials.gov: NCT04642105). We will study the prevalence of epileptic seizures and sleep-wake disturbances in Alzheimer's disease using this wearable (ClinicalTrials.gov: NCT03617497) and tonic, atonic and myoclonic seizures in childhood epilepsy (ClinicalTrials.gov: NCT04584385). Development of improved seizure detection algorithms based on artificial intelligence and machine learning will be an essential step to integrate this wearable into everyday clinical practice of the neurologist-epileptologist to improve management of patients with refractory focal epilepsy.

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Disclosure of Conflicts of Interest

None of the authors has any conflicts of interest to disclose.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

[1] Forsgren L, Beghi E, Oun A, Sillanpää M. The epidemiology of epilepsy in Europe—a systematic review. Eur J Neurol. 2005; 12: 245– 53.

[2] French JA. Refractory epilepsy: clinical overview. Epilepsia. 2007; 48: 3– 7.

[3] Elger CE, Mormann F. Seizure prediction and documentation—two important problems. Lancet Neurol. 2013; 12: 531– 2.

[4] Blum DE, Eskola J, Bortz JJ, Fisher RS. Patient awareness of seizures. Neurology. 1996; 47: 260– 4.

[5] Fisher RS, Blum DE, DiVentura B, et al. Seizure diaries for clinical research and practice: limitations and future prospects. Epilepsy Behav. 2012; 24: 304– 10.

[6] Hoppe C, Poepel A, Elger CE. Epilepsy: accuracy of patient seizure counts. Arch Neurol. 2007; 64: 1595– 9.

[7] Poochikian-Sarkissian S, Tai P, del Campo M, et al. Patient awareness of seizures as documented in the epilepsy monitoring unit. Can J Neurosci Nurs. 2009; 31: 22– 3.

[8] Tatum WO, Winters L, Gieron M, et al. Outpatient seizure identification: results of 502 patients using computer-assisted ambulatory EEG. J Clin Neurophysiol. 2001; 18: 14– 9.

[9] Gu Y, Cleeren E, Dan J, et al. Comparison between scalp EEG and behind-the-ear EEG for development of a wearable seizure detection system for patients with focal epilepsy. Sensors. 2017; 18: 1– 19.

[10] Vandecasteele K, De Cooman T, Dan J, et al. Visual seizure annotation and automated seizure detection using behind-the-ear electroencephalographic channels. Epilepsia. 2020;61(4):766-775.

[11] Devinsky O, Kelley K, Porter RJ, Theodore WH. Clinical and electroencephalographic features of simple partial seizures. Neurology. 1988; 38: 1347– 52.

[12] Foldvary N, Klem G, Hammel J, Bingaman W, Najm I, Lüders H. The localizing value of ictal EEG in focal epilepsy. Neurology. 2001 Dec 11;57(11):2022-8.

[13] Walczak TS, Radtke RA, Lewis DV. Accuracy and interobserver reliability of scalp ictal EEG. Neurology. 1992 Dec;42(12):2279-85.

[14] Spencer SS, Williamson PD, Bridgers SL, Mattson RH, Cicchetti DV, Spencer DD. Reliability and accuracy of localization by scalp ictal EEG. Neurology. 1985 Nov;35(11):1567-75.

[15] Pavei J, Heinzen RG, Novakova B, et al. Early Seizure Detection Based on Cardiac Autonomic Regulation Dynamics. Front Physiol. 2017;8:765.

[16] De Cooman T, Varon C, Hunyadi B, Van Paesschen W, Lagae L, Van Huffel S. Online automated seizure detection in temporal lobe epilepsy patients using single-lead ECG. Int J Neural Syst. 2017; 27: 1750022.

[17] Jeppesen J, Fuglsang-Frederiksen A, Johansen P, Christensen J, Wüstenhagen S, Tankisi H, et al. O-45 automated seizure detection for epilepsy patients using wearable ecg-device. Neurophysiol Clin. 2019;130(7): p. e36

[18] Vandecasteele K, De Cooman T, Gu Y, et al. Automated epileptic seizure detection based on wearable ECG and PPG in a hospital environment. Sensors. 2017; 17: 2338.

[19] Eggleston KS, Olin BD, Fisher RS. Ictal tachycardia: the head-heart connection. Seizure. 2014; 23: 496– 505.

[20] Zijlmans M, Flanagan D, Gotman J. Heart rate changes and ECG abnormalities during epileptic seizures: prevalence and definition of an objective clinical sign. Epilepsia. 2002;43(8):847-854.

[21] Chen W, Guo CL, Zhang PS, et al. Heart rate changes in partial seizures: analysis of influencing factors among refractory patients. BMC Neurol. 2014;14:135.

[22] Fürbass F, Kampusch S, Kaniusas E, et al. Automatic multimodal detection for long-term seizure documentation in epilepsy. Clin Neurophysiol. 2017; 128: 1466– 72.

[23] Qaraqe M, Ismail M, Serpedin E, Zulfi H. Epileptic seizure onset detection based on EEG and ECG data fusion. Epilepsy Behav. 2016;58:48-60.

[24] Cogan, D., Birjandtalab, J., Nourani, M., Harvey, J., & Nagaraddi, V. Multi-Biosignal Analysis for Epileptic Seizure Monitoring. International Journal of Neural Systems. 2017;27(01), 1650031.

[25] Beniczky S, Ryvlin P. Standards for testing and clinical validation of seizure detection devices. Epilepsia. 2018;59 Suppl 1:9-13.

[26] Klatt J, Feldwisch-Drentrup H, Ihle M, et al. The EPILEPSIAE database: an extensive electroencephalography database of epilepsy patients. Epilepsia. 2012;53(9):1669-1676.

[27] Ihle M, Feldwisch-Drentrup H, Teixeira CA, et al. EPILEPSIAE - a European epilepsy database. Comput Methods Programs Biomed. 2012;106(3):127-138.

[28] Seeck M, Koessler L, Bast T, et al. The standardized EEG electrode array of the IFCN. Clin Neurophysiol. 2017;128(10):2070-2077.

[29] Li C, Zheng C, Tai C. Detection of ECG characteristic points using wavelet transforms. IEEE Trans Biomed Eng. 1995;42(1):21-28.

[30] Varon C, Caicedo A, Testelmans D, Buyse B, Van Huffel S. A Novel Algorithm for the Automatic Detection of Sleep Apnea From Single-Lead ECG. IEEE Trans Biomed Eng. 2015;62(9):2269-2278.

[31] De Cooman T, Goovaerts G, Varon C, Widjaja D, Willemen T, Van Huffel S. Heart beat detection in multimodal data using automatic relevant signal detection. Physiol Meas. 2015;36(8):1691-1704.

[32] Jeppesen J, Beniczky S, Johansen P, Sidenius P, Fuglsang-Frederiksen A. Detection of epileptic seizures with a modified heart rate variability algorithm based on Lorenz plot. Seizure. 2015;24:1-7.

[33] Doyle OM, Temko A, Marnane W, Lightbody G, Boylan GB. Heart rate based automatic seizure detection in the newborn. Med Eng Phys. 2010;32(8):829-839.

[34] Orphanidou C, Bonnici T, Charlton P, Clifton D, Vallance D, Tarassenko L. Signal-quality indices for the electrocardiogram and photoplethysmogram: derivation and applications to wireless monitoring. IEEE J Biomed Health Inform. 2015;19(3):832-838.

[35] Johnson AE, Behar J, Andreotti F, Clifford GD, Oster J. Multimodal heart beat detection using signal quality indices. Physiol Meas. 2015;36(8):1665-1677.

[36] Ganeshapillai G, Liu JF, Guttag J. Reconstruction of ECG signals in presence of corruption. Annu Int Conf IEEE Eng Med Biol Soc. 2011;2011:3764-3767.

[37] Citi L, Klerman E, Brown E, Barbieri R. Point Process Heart Rate Variability Assessment during Sleep Deprivation. Comput Cardiol (2010). 2010;37:721-724.

[38] Osorio I. Automated seizure detection using EKG. Int J Neural Syst. 2014;24(2):1450001.

[39] Osorio I, Manly BF. Is seizure detection based on EKG clinically relevant?. Clin Neurophysiol. 2014;125(10):1946-1951.

[40] Ungureanu C, Bui V, Roosmalen W, Aarts RM, Arends JB, Verhoeven R, et al. A wearable monitoring system for nocturnal epileptic seizures. In 2014 8th International Symposium on Medical Information and Communication Technology (ISMICT). 2014 (pp. 1-5). IEEE.

[41] Deviaene M, Testelmans D, Borzee P, Buyse B, Huffel SV, Varon C. Feature Selection Algorithm based on Random Forest applied to Sleep Apnea Detection. Annu Int Conf IEEE Eng Med Biol Soc. 2019;2019:2580-2583.

[42] Ben-David A. Comparison of classification accuracy using Cohen's Weighted Kappa. Expert Syst Appl.34.2 (2008): 825-832.

[43] I. Mobile Devices and Health. N Engl J Med. 2019;381(10):956-968.

[44] Kurada AV, Srinivasan T, Hammond S, Ulate-Campos A, Bidwell J. Seizure detection devices for use in antiseizure medication clinical trials: A systematic review. Seizure. 2019 Mar;66:61-69.

[45] Verdru J, Van Paesschen W. Wearable seizure detection devices in refractory epilepsy. Acta Neurol Belg. 2020 Dec;120(6):1271-1281.

[46] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, Hirsch E, Jain S, Mathern GW, Moshé SL, Nordli DR, Perucca E, Tomson T, Wiebe S, Zhang YH, Zuberi SM. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):512-521.

[47] De Cooman T, Vandecasteele K, Varon C, et al. Personalizing Heart Rate-Based Seizure Detection Using Supervised SVM Transfer Learning. Front Neurol. 2020;11:145.

[48] Becker, T.; Vandecasteele, K.; Chatzichristos, C.; Van Paesschen, W.; Valkenborg, D.; Van Huffel, S.; De Vos, M. Classification with a Deferral Option and Low-Trust Filtering for Automated Seizure Detection. Preprints Sensors. 2020.

Tables

TABLE I: A. Sensitivity (%) for the unimodal EEG and ECG at a FAR of 1 FP/hour for the different databases. B. Sensitivity (%) of the multimodal (at a threshold generating 1FP/h for the unimodal modalities) and EEG-based detectors at the same FAR for the different databases. Mean ± standard deviation (median [min max]) are shown in the table.

A.

	Unimodal EEG	Unimodal ECG
SeizeIT1	84 ± 26 (100 [0 100])	68 ± 32 (72 [0 100])
Epilepsiae - Freiburg	77 ± 26 (85 [0 100])	74 ± 23 (79 [12 100])
Epilepsiae – Paris	82 ± 28 (100 [0 100])	52 ± 33 (50 [0 100])

B.

	Multimodal	Unimodal EEG
SeizeIT1	95 ± 11 (100 [60 100])	85 ± 26 (100 [0 100])
Epilepsiae - Freiburg	90 ± 14 (100 [50 100])	82 ± 25 (88 [6 100])
Epilepsiae – Paris	84 ± 27 (100 [0 100])	84 ± 26 (100 [0 100])

Table II: Sensitivity (%), specificity (%), percentage of false detections due to artifacts according to the two readers and the Cohen's Kappa value were calculated for the two training sessions (Training 1 and Training 2) and the three databases. The mean +- standard deviation, median [min max] was shown.

	Sens (%)		Spec (%)		Artifacts (%)		Kappa
	Reader 1	Reader 2	Reader 1	Reader 2	Reader 1	Reader 2	
Training 1	71 ± 23	79 ± 10	80 ± 11	81 ± 29	-	-	0.62 ± 0.12
	83 [44 86]	83 [67 86]	84 [68 88]	96 [48 100]			0.67 [0.49 0.71]
Training 2	83 ± 17	58 ± 22	88 ± 6	90 ± 13	-	-	0.66 ± 0.02
	83 [67 100]	67 [33 75]	86 [83 95]	95 [75 100]			0.67 0.[64 0.68]
Epilepsiae - Freiburg	70 ± 26	77 ± 23	85 ± 12	89 ± 9	35 ± 14	39 ± 11	0.55 ± 0.26
	67 [25 100]	75 [33 100]	88 [64 100]	92 [64 100]	33 [13 67]	42 [18 61]	0.61 [0.11 1]
Epilepsiae - Paris	87 ± 23	81 ± 31	87 ± 12	91 ± 7	56 ± 30	53 ± 29	0.54 ± 0.26
	100 [33 100]	100 [0 100]	88 [60 100]	92 [80 100]	64 [0 100]	64 [0 92]	0.51 [0.4 1]
SeizeIT1	89 ± 17	81 ± 22	83 ± 21	93 ± 7	18 ± 20	28 ± 26	0.76 ± 0.32
	100 [67 100]	83 [50 100]	96 [57 100]	96 [83 100]	9 [0 48]	15 [4 63]	0.92 [0.29 1]
All	**80 ± 24**	**78 ± 25**	**85 ± 13**	**90 ± 10**	**42 ± 27**	**44 ± 24**	**0.59 ± 0.25**
	93 [25 100]	**85 [0 100]**	**88 [57 100]**	**92 [48 100]**	**39 [0 100]**	**42 [0 92]**	**0.62 [0.04 1]**

Figure legends

Figure 1: The behind-the-ear EEG and ECG are shown during a temporal focal impaired awareness seizures from the right hemisphere. The top figure contains 4 channels: channel 1: crosshead, channel 2: left channel, channel 3: right channel, channel 4: ECG. The amplitude of the ECG signal is decreased with a factor 10. The seizure onset is depicted with a vertical black line at 10 seconds. The left bottom figure shows the extracted heart rate in beats per minute

during the seizure. A heart rate increase from 40 to 80 beats per minute is observed. The right bottom figure shows a close-up of the behind-the-ear EEG channel during 20 – 30 seconds after the seizure onset.

Figure 2: An overview of the seizure type (a), localization (b), lateralization (c) and seizure duration (d) for the three different datasets [Abbreviations: FIA, focal impaired awareness; FA, focal aware; F-BTC, focal to bilateral tonic-clonic; UC, unclassified; NC, not clear; F, frontal; T, temporal; P, parietal; O, occipital; Fronto-T, fronto-temporal; Fronto-P, fronto-parietal; Temporo-P, temporo-parietal; Temporo-O, temporo-occipital; Parieto-O, parieto-occipital; bi, bilateral]

Figure 3: Example of three seizure segments, their average pattern and two false alarms from one patient with left posterotemporo-occipital epilepsy. The seizure onset or false detection onset is depicted with a horizontal black line. This patient had three different seizures types: FIA, UC and FA. False alarm 1 is due to artifacts and false alarm 2 has a physiological heart rate increase. Subplot 1 contains the filtered ECG with a bandpass filter [1 – 45 Hz], together with the extracted R-peaks (red circles) [zoomed in]. Subplot 2 contains the extracted heart rate (HR) in beats per minute.

Figure 4: Sensitivity in function of FAR for the different datasets. The blue graph depicts the unimodal results of EEG, the red one the results of ECG. On those graphs, the sensitivities at a FAR at 0.2 FP/hour, 0.5 FP/hour and 1 FP/hour are depicted with circles. The black points are the results of the multimodal algorithm at three discrete thresholds (square: 0.2 FP/hour, diamond: 0.5 FP/hour and star: 1FP/hour). For comparison, the results on the EEG graph with the same FAR are indicated with blue marks.

Figure 5 (appendix): Performance comparison of our proposed ECG-based seizure detection algorithm. The sensitivity versus FAR is plotted together with the standard deviation on the sensitivity [dotted lines]. The sensitivity and FAR is shown for two state-of-the-art solutions: Fürbass[22] and De Cooman[16] et al., the dotted lines indicate the standard deviation in two directions: the FAR and sensitivity.

Figure 6: Percentage of detected seizures at a FAR of 1/hour is displayed for the four groups: Seizures detected with both EEG and ECG, only with EEG, only with ECG or seizures not detected neither with EEG nor with ECG in function of Seizure type (A) and in function of localization (B). The number of seizures in each group is indicated in the legend.

Supporting information

Appendix A: The Unimodal ECG model: comparison with state-of-the-art

1. Methods

The performance of our developed ECG-based seizure detection algorithm was compared with two other ECG-based seizure detection algorithms, De Cooman and colleagues[16] and Fürbass and colleagues[22]. Note that the developed algorithm is designed for offline usage and the state-of-the-algorithms[16,22] can be used for real-time alarming. The Epilepsia - Freiburg database was used for comparison, since this data was not used for the algorithm development (in order to avoid any overfit concern). To compare the ECG-based algorithm with state-of-the-art patient-independent algorithms, a ‘sensitivity in function of FAR’ was constructed. The performance of the whole dataset was calculated for every cut-off probability value.

2. Results

In Figure 5, the performance is compared to two state-of-the-art ECG-based seizure detection algorithms. Fürbass and colleagues[22] achieved a sensitivity of 39.35% with an FAR of 0.18 per hour. With the same FAR, our algorithm had a sensitivity of 48.7%. De Cooman and colleagues[16] achieved a sensitivity of 71.02% with 2.43 FP/hour, whereas our algorithm had a sensitivity of 84.1% with the same FAR.

3. Discussion

Increased sensitivities were observed by comparing to two state-of-the-art algorithms with the same FARs.

Appendix B: ECG features

We list here the used features for the proposed ECG-based seizure detection. Please refer to the given references for detailed descriptions of the different mentioned features.

A. Time domain HRV features

Each R-peak is detected and the so-called normal-to-normal (NN) intervals, which are the time intervals between adjacent R-peaks)

1) The mean NN interval

2) The standard deviation of the NN intervals (SDNN)

3) The ratio of the standard deviation of NN intervals and mean NN interval

4) The difference between feature value 1 of the current window and its value of the previous window

5) The difference between feature value 2 of the current window and its value of the previous window

6) The difference between feature value 3 of the current window and its value of the previous window

7) The root mean square of successive difference (RMSSD) of the NN intervals

8) Percentage of the difference in two successive NN intervals that is larger than 0.005 seconds

9) Percentage of the difference in two successive NN intervals that is larger than 0.01 seconds

10) Percentage of the difference in two successive NN intervals that is larger than 0.015 seconds

11) Percentage of the difference in two successive NN intervals that is larger than 0.02 seconds

12) Percentage of the difference in two successive NN intervals that is larger than 0.025 seconds

13) The standard deviation of the successive differences between adjacent NN intervals

14) The maximum value of the successive differences between adjacent NN intervals

15-26) Feature 1,2,3,7,8,9,10,11,12,13,14,15 of the previous window

27-38) Feature 1,2,3,7,8,9,10,11,12,13,14,15 of the next window

B. Frequency domain HRV features

39) The absolute power in the very low frequency (VLF) component (0-0.04 Hz).

40) The absolute power in the low frequency (LF) component (0.04 - 0.15 Hz).

41) The absolute power in the high frequency (HF) component (0.15 - 0.4 Hz).

42) The logarithm of the total power.

43) The ratio between LF and HF.

44) The ratio between VLF and HF.

45) The Shannon entropy of the NN intervals

46) The Shannon entropy on the power spectral density values of the ECG signal

47 – 54) Feature 46, 47, 48, 49, 50, 51, 52, 53 of the previous window

55 – 62) Feature 46, 47, 48, 49, 50, 51, 52, 53 of the next window

C. Features Jeppesen et al.[31]

Features were derived from the Lorenz plot (or Poincaré plot).

63) The standard deviation SD1 of the transverse direction of the Lorenz plot.

64) The standard deviation SD2 of the longitudinal direction of the Lorenz plot.

65) The ratio of SD2 and SD1

66) The logarithm of the product of SD1 and SD2

67) The modified cardiac sympathetic index (CSI), Calculated by L2=T with T four times the standard deviation of the spread in the transverse axis and L four times the standard deviation of the spread in the longitudinal axis

D. Features Doyle et al.[32]

68) The del+ feature is computed using sequential trend analysis, which involves plotting the first derivative of the NN intervals as a function of the immediately preceding one. Del+ is the concentration of points in the first quadrant (+/+ axis)

69) The del- feature is the concentration of points in the 3rd quadrant (-/- axis)

70) The line length of the ECG signal

71) The number of zero-crossings of the ECG signal

E. Features De Cooman et al.[16]

Features were derived from the heart rate increases (HRI), occurring in the specific time window.

72) The maximal duration of the HRI in number of heart beats

73) The maximal slope (or heart rate gradient) during the HRI

74) The maximal HR obtained during the HRI

75) The signal quality index, based on RR matching [30]

76) The heart rate at the start of the HRI

77) The duration of HRI in seconds

78) The ratio of the maximum heart rate and the average heart rate during the HRI

79) The difference between the peak heart rate and the heart rate at the start of the HRI

80) The heart rate at the end of the HRI

81) The mean heart rate after the HRI when the new baseline is reached

82) The needed time to reach the new baseline

83) The average HR before the HRI

84) The ratio of the mean HR after the HRI and mean HR before the HRI

85 – 90) The number of heart beats higher than 110%, 120%, 130%, 140%, 150% and 160% of the mean HR before the HRI

91 – 95) The number of the heart beats higher than 20, 30, 40, 50, 60 bpm + mean HR before HRI

F. Circadian Rhythm Features

Heart rate characteristics fluctuate throughout the day which is called the circadian rhythm. Circadian features are extracted.

96) The mean value of the circadian NN intervals

97) The standard deviation of the circadian NN intervals

98) The ratio between feature 98 and 97

99) The root mean square of successive differences of the circadian NN intervals

100) The standard deviation of successive differences of the circadian NN intervals

101) The mean value of successive differences of the circadian NN intervals

102) The maximum value of the successive differences of the circadian NN intervals

G. Features related to the noise level[34]

103) The maximum value of the kurtosis, calculated based on the previous 10 seconds

104) The minimum value of the kurtosis, calculated based on the previous 10 seconds

105) The mean value of the kurtosis, computed on 10 seconds windows

106) The fusion signal quality index (FSQI) determines whether the ECG segment is of low or high quality based on the level of agreement of two heart peak detectors[34]

107) The relative power of the powerline interference at 50Hz and harmonics

108) The relative power of the high frequency noise

109) The ECGSQI provides a signal quality estimate of an ECG signals[35]

H. Point process features

Point process features[36]

110) The mean spectral power.

111) The maximum spectral low-frequency power.

112) The maximum spectral high-frequency power.

113) The maximum value of the ratio of the spectral low frequency power and the spectral high-frequency power

114) The maximum spectral power.

115) The mean very low frequency (VLF) power.

116) The mean low frequency (LF) power.

117) The mean high frequency (HF) power.

118) The ratio of the mean low frequency (LF) power and mean high frequency (HF) power.

I. Features Osorio et al.[37,38]

119) The maximum threshold value for the R peak detection of the ECG signal

120) The duration in which the HR in the current window is higher than 115% of the average HR in the reference window in the past

121) The duration in which the HR in the current window is higher than 120% of the average HR in the reference window in the past

122) The duration in which the HR in the current window is higher than 125% of the average HR in the reference window in the past

123) The duration in which the HR in the current window is higher than 130% of the average HR in the reference window in the past

124) The maximum value of the short-term window.

125) The average value of the heart rate in a long-term window

126) The standard deviation of the heart rate in a long-term window

J. Features Ungureanu et al.[39]

127) The age of the patient

128) The maximum value of a tachycardiac event (CS+)

129) The minimum value of a bradycardic event (CS-)

130) The threshold of the algorithm based on age

131) The maximum duration of positive values exceeding a positive threshold

132) The maximum duration of negative values exceeding a negative threshold

Appendix C: Detected seizures in function of seizure type and localization

Figure 6 shows the percentage of detected seizures at a FAR of 1/hour for the modalities in function of seizure type (A) and localization (B). The percentage of seizures detected both with EEG and ECG was the highest for F-BTC seizures (74%) and the lowest for FA seizures (32%). The percentage detected with EEG only was the highest for UC seizures (34%), for ECG only this percentage was the highest for the FA group (13%). FA seizures have also the highest percentage of seizures not detected with any of the two modalities (26%). The percentage of seizures detected both with EEG and ECG was the highest for seizures with a (fronto/temporo)-parietal origin (60%), followed with the temporal (59%) and (temporo/parieto)-occipital origin (59%). Seizures with a frontal origin have the highest percentage of seizures detected with EEG only (41%), whereas the lowest percentage with ECG only (3%). The seizures with an unclear origin have the highest percentage of seizures not detected with any of the two modalities (20%), followed by the fronto-temporal seizures (18%) and (fronto/temporo)-parietal seizures (18%).

Appendix D: Probable reasons why seizures are not detected with EEG, while they are detected with ECG

53 seizures (6%) were detected only with ECG, which exhibits the added value of ECG in this study. 28 seizures (10%), 12 seizures (7%) and 13 seizures (3%) were detected only with ECG from Epilepsiae-Freiburg, SeizeIT1 and Epilepsiae-Paris. Probable reasons why those seizures could not be picked up with EEG are listed.

- Artifacts were present (14 seizures): strong artifacts with electrode disconnection was observed during 1 seizure, strong artifacts without visible ictal patterns were present during 5 seizures, artifacts with some ictal patterns could be seen during 8 seizures.
- No typical ictal pattern could be observed or the difference with the background EEG was minimal (11 seizures).
- No EEG correlates were observed (10 seizures). Only in the Epilepsiae - Freiburg database, seizures were present without any EEG correlates on full scalp.
- Seizures were not visible on the behind-the-ear electrodes, marked by a neurologist (5 seizures).
- There was no propagation to the temporal lobe, which was annotated in the Epilepsiae database (4 seizures).
- The seizure duration was shorter than 10 seconds. Due to the postprocessing rules, those seizures will be not detected (3 seizures).
- Some patterns are difficult to detect (for example: low amplitude fast activity). This is especially difficult when the majority of the patients' seizures have other patterns (3 seizures).
- Only 2 seizures were available per patient, as a result only one seizure is available to train the model and overfitting occurs (3 seizures).