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Patient-Specific Early Seizure Detection from Scalp EEG

Georgiy R. Minasyan¹, John B. Chatten¹, Martha Jane Chatten¹, and Richard N. Harner²

¹ Chatten Associates, Inc, West Conshohocken, PA, USA

² Brain Vue Systems, Philadelphia, PA, USA

Abstract

Objective—Develop a method for automatic detection of seizures prior to or immediately after clinical onset using features derived from scalp EEG.

Methods—This detection method is patient-specific. It uses recurrent neural networks and a variety of input features. For each patient we trained and optimized the detection algorithm for two cases: 1) during the period immediately preceding seizure onset, and 2) during the period immediately following seizure onset. Continuous scalp EEG recordings (duration 15 – 62 h, median 25 h) from 25 patients, including a total of 86 seizures, were used in this study.

Results—Pre-onset detection was successful in 14 of the 25 patients. For these 14 patients, all of the testing seizures were detected prior to seizure onset with a median pre-onset time of 51 sec and false positive rate was 0.06/h. Post-onset detection had 100% sensitivity, 0.023/hr false positive rate and median delay of 4 sec after onset.

Conclusions—The unique results of this study relate to pre-onset detection.

Significance—Our results suggest that reliable pre-onset seizure detection may be achievable for a significant subset of epilepsy patients without use of invasive electrodes.

Keywords

Epilepsy; Early Seizure Detection; Recurrent Neural Networks; Scalp EEG

1. Introduction

1.1 Early seizure detection

Seizure detection is considered an important problem for several reasons. Long-term EEG (and video) recording has become essential to aid in the localization of epileptic foci for surgical removal. Automatic seizure detection was originally developed to aid in the review of voluminous continuous EEG/video recording (Gotman and Gloor, 1979). More recently early seizure detection during EEG monitoring setting has become necessary for ictal SPECT localization. So far this application has depended on early patient, nurse, observer recognition of seizure onset. This process can be improved and extended by the addition of automatic seizure detection prior to seizure onset, “pre-onset detection”. With advances in electronic miniaturization there is now increasing interest in the development of wearable devices that can provide pre-onset detection to serve as a warning for self protection, caretaker notification or for local closed-loop brain stimulation or anticonvulsant injection to suppress seizure activity locally before it becomes widespread or has major clinical expression.

Over the past decade, significant theoretical and experimental efforts, as well as many papers have been focused on developing computerized methods for epileptic seizure prediction and early onset detection. These efforts were reviewed by Litt and Echauz (2002), Iasemidis (2003), Maiwald et al. (2004), Mormann et al. (2006, 2007), Schad et al. (2008), Hughes (2008), Andrzejac et al. (2009). Using a wide variety of linear and nonlinear/dynamical system methods, these studies have shown that seizure anticipation is possible in certain circumstances, most convincingly when intracranial hippocampal EEG signals are analyzed in patients with mesial temporal epilepsy. The results with intracranial EEG recordings from epileptic foci in other locations are less good, and results from scalp EEG recordings have been particularly discouraging for long-term seizure anticipation.

As the nonlinear dynamics-based EEG classification work has progressed, the limitations of available computational procedures have become increasingly apparent, particularly when confronted with long-term nonstationarity and excessive noise from multiple electrical and physiologic sources. The latter limitation is very important in the case of scalp EEG, which is often contaminated by EMG noise, eye blinks, etc. In order to overcome these difficulties, alternative measures reflecting short-term signal “textural complexity” changes that precede seizures have been employed by a number of investigators within a linear system framework. For example, Petrosian et al. (1996, 1997, 2000) have explored the ability of specifically designed and trained recurrent neural networks (RNN) combined with wavelet decomposition preprocessing to predict seizures. The RNN approach is particularly useful for the task of patient specific EEG prediction because it can be trained in a straightforward manner, is able to implement extremely nonlinear decision boundaries and possesses memory of previous states. Their initial result (from a single patient) indicates that a scalp-recorded seizure could be predicted 2 min prior to onset (Petrosian et al., 1997). A similar wavelet-based approach was used by Geva and Kerem (1998) to forecast generalized epileptic seizures induced by hyperbaric oxygenation of rats. Instead of RNN training they used an unsupervised optimal fuzzy clustering algorithm together with the extracted wavelet parameters in order to determine an optimal number of classes describing the current EEG feature pattern and to detect an abrupt and considerable change in the number.

More success has been achieved in detecting seizures immediately after onset (e.g. within 10 s of onset). There are 3 major difficulties in the detection of a seizure at earliest onset (Gotman and Qu, 1997): (1) onset patterns are highly variable from one patient to another; (2) the onset often involves small changes and evolves gradually into a full seizure pattern during a period which can last 20 seconds or more; and (3) the onset pattern in one patient can be very similar to non-seizure patterns of another patient. In order to overcome those difficulties, Qu and Gotman (1995, 1997) designed a patient-specific algorithm to detect seizure onsets. They took a small set of features extracted from the time and frequency domains from a single seizure and used a modified nearest-neighbor classification technique to detect subsequent seizures in the same patient. Using seizures from 12 patients, their system reached an onset detection rate of 100% with an average delay of 9.35 seconds after onset.

Another group (Osorio et al., 1998) achieved early onset detection of electrographic seizures in intracranial EEG recordings using a simple band-limited energy-based thresholding approach combined with median filtering to remove short-term transient artifacts. The “adaptation” of widening the bandpass to include lower frequencies allowed some seizures missed by their generic algorithm to be detected (Osorio et al., 2002).

Shoeb et al. (2004, 2005) presented a patient-specific seizure onset detector using 64 features extracted from scalp EEG by means of 7-level wavelet decomposition. The classification stage of the seizure detector is based on the support vector machines (SVM) technique. Their method had 94 % sensitivity, false alarm rate of 0.25/h and detection delay of 8 $\pm$ 3.2 seconds after

the electrographic onset. Similar performance has been reported by recent work of Meier et al. (2008). The authors designed SVM-based, “generic” seizure detector by taking into account the seizure morphology. Wilson (2005) used a probabilistic neural network for patient specific seizure detection. These papers suggest the feasibility of useful, real-time automatic early seizure onset detection from scalp EEG but also underline the need for improved sensitivity/specificity in order to achieve maximum clinical utility. In the case of scalp EEG, patient-specific algorithms are required to achieve high levels of reliability. None of the published papers demonstrated feasibility of pre-onset seizure detection.

1.2 Problem and approach

The problem is to develop a highly reliable method to detect seizure onsets in time to take effective evasive, diagnostic or therapeutic action, ideally prior to the onset of clinical symptoms, with rare or no false warnings to diminish the significance of a warning signal. In this study, we have limited our investigations to scalp EEG.

We have approached the problem first by noting the value of parameters based on the EEG waveform. Second, we have recognized the potential value of spectral, time-domain and wavelet analysis parameters in summarizing activities not clearly expressed as waveform alteration. Third, we added several complexity measures to characterize the EEG epoch as a whole. Fourth, in order to combine what now becomes a large set of parameters, we use neural net technology to analyze individual channels, along with expert supervision to combine parameters and channels. The use of an overcomplete (redundant) parameter set, requires multiple possible outcomes for maximum efficiency so we look for not only ictal but also preictal, postictal and interictal (including waking, moving, sleeping and noisy patterns) states. Finally, because seizure patterns tend to vary widely across patients, but tend to be stereotypic in an individual patient, we chose to develop this system to adapt to individual patients.

2. Methods

The seizure pre-onset detection method has a modular design, and each module has a specific function. The modules are as follows:

- *Feature Extraction Module.* The first module extracts features from the raw EEG data using spectral, wavelet, time domain analysis and complexity measures, and produces feature vectors.
- *Feature Selection Module.* This module analyses features extracted by the first module and automatically removes irrelevant and redundant parameters. The output of this module produces a reduced feature set for input to the RNN.
- *Recurrent Neural Network.* The third module is the neural network-based classifier. RNN classifies each EEG epoch into one of five states.
- *Decision-Making Module.* This module combines individual RNN outputs, in space-time, declaring a “Pre-onset Detection” when conditions are met. A second output can be configured to provide an “Onset Detection”.

The overall diagram of the algorithm is presented in Figure 1. The detector uses a set of RNNs, one per EEG channel. Each RNN was individually trained to remember the specific EEG patterns for this channel. Two of the RNN output nodes (the Preictal and Ictal nodes) are used as separate detection systems. The preictal node is devoted to recognizing pre-ictal or “pre-onset patterns”. The ictal node detects seizure onset patterns. Space-time post-processing then is performed independently in the Decision-Making Module for each detector in order to reject false alarms and to build a robust decision statistic. Preictal outputs are combined to create Pre-onset Detection events and Ictal outputs are combined to create Onset Detection events. We

define seizure pre-onset patterns as the pre-ictal activity in the first 60 s preceding EEG onset (EO) and onset patterns as the ictal activity in the 1–2 minutes following EO.

2.1 Database

The EEG data were obtained from 25 epilepsy patients hospitalized for long-term EEG monitoring as part of pre-surgical evaluation of seizure pattern and localization in five cooperating centers including Thomas Jefferson University, Dartmouth University, University of Virginia, UCLA and University of Michigan medical centers. Continuous multichannel recordings typically 24 or more hours in duration were used. All of the 25 patients had localization-related epilepsy and most ranged in age from 20 to 40 years (single outliers at 5 and 58 yr). All of these patients were on monitoring protocols that included reduction of anticonvulsant medications to encourage the occurrence of habitual seizure types in the shortest possible time consistent with patient safety. Patient selection criteria were the following:

- Patient should have two or more seizures
- Patient must have a single type of seizure morphology

Most of the patients met these criteria. Some patients were rejected because insufficient number of seizures or multiple seizure types. Bad quality recordings due to electrode or other artifacts were also excluded. EMG or movement artifact was not a basis of exclusion. The following seizure types were represented in our study: rhythmic activity in delta, theta, alpha and beta range, poly-spikes, rhythmic sharp waves.

EEG sections containing seizure and non-seizures activity for training, validation and testing were selected consecutively. If training with first seizure was not successful then two consecutive seizures were used for training. Across the 25 patients actually used in the study there were a total 86 seizures. Table 1 gives the distribution of uses of these seizures for each patient. “Training seizures” are defined as seizures used for training the single-channel RNNs. “Validation seizures” are defined as seizures used to optimize the overall recognition algorithm including the decision making module, but are not used for RNN training. “Testing seizures” are those used to test performance of the algorithm as developed and optimized on the training and validation seizures. The cases where there are zero validation seizures are those patients for which no optimization was necessary. Standard defaults parameters sufficed. In designing the pre-onset detectors, validation seizure samples were required in 11 patients to get acceptable performance. The onset detector did not need an additional seizure for optimization.

2.2 Recording

The scalp EEG data were recorded using 64-channel Grass-Telefactor Beehive LTM system with the international 10/20 montage at a sampling rate of 200 Hz and digitized with 12 bits. Data were filtered with a high-pass filter of 0.3 Hz and a low-pass filter of 70 Hz with narrow 60 Hz trap. Recording lengths varied from 15 to 62 hours. The number of channels varied from 20 to 32. In several patients, EKG and sphenoidal electrodes were used in addition to the standard EEG (scalp) electrodes. One case had simultaneous recording from 26 depth locations as well. The depth electrode channels were not used.

2.3 Parameters

Success of any pattern recognition system depends on the appropriate selection of parameters or features. Seizures can cause a variety of patterns in the scalp EEG, and many candidate features have been considered in the literature. We use a large predefined feature library which consists of spectral, wavelet, autoregressive (AR) and waveform parameters to characterize the EEG patterns of various interictal, preictal, ictal, and postictal states.

We selected a master list of 58 features by analyzing the utility of candidate features in detecting various EEG patterns in a number of patients. Many of these clearly contribute differently in specific patients according to their idiosyncratic interictal, pre-ictal, and ictal patterns. Many features from our list have been also used by other authors to predict or detect seizures (Gotman and Qu, 1997; Khan and Gotman, 2003; Esteller et al., 1999; Franaszczuk et al., 1998; D'Alessandro et al, 2005, Subasi 2007) or detect spikes and sharp waves (Goelz et al., 2000; Gotman and Wang, 1991). We chose an EEG epoch of 2.56 s long containing 512 samples for each channel. The 58 features extracted from each EEG epoch are divided into the following four groups. A full list of features and details of feature extraction is described in an Appendix.

2.3.1 Spectral parameters—This group include: relative power in delta (0–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), sigma (12–16 Hz), beta1 (16–20 Hz), beta2 (20–24 Hz), beta3 (24–28 Hz) and beta4 (28–32 Hz) and in the high frequency band (32–70 Hz), mean frequency, peak frequency and bandwidth of the peak frequency. This set of parameters was used to capture information regarding rhythmic EEG background, ictal and muscle activity.

2.3.2 Time domain parameters—Time domain parameters are based on amplitude and duration of half-waves. We included the morphological features set used in the Grass-Telefactor SzAC™ seizure and spike detector (Gotman and Gloor, 1976; Gotman, 1982) and by Qu and Gotman (1997). These parameters (average duration of half-waves, coefficients of variation of half-waves duration and amplitude), have provided useful seizure detection in routine video/EEG monitoring applications that do not require reliable detection of early seizure onset or high specificity. The half-wave decomposition methods are more robust than spectral methods when strong low-frequency components or high-frequency noise are present. In addition to half-wave based parameters, the nonlinear energy operator has been used. The average of nonlinear energy is a measure of energy proportional both to signal amplitude and frequency, and is a useful indicator of instantaneous changes of the frequency content.

2.3.3 Wavelet analysis parameters—Wavelet coefficients reflect the combined effect of large fluctuations of the epoch and a good matching of a shape between the signal and the wavelet. We rely on the wavelet features to characterize localized waveforms such as spikes, sharp waves, and K-complexes, in addition to slow waves and low frequency artifacts. Wavelet multilevel decomposition using Daubechies wavelet (DAUB4, Daubechies, 1992) is performed on each 2.56 s epoch. The number of scales (decomposition levels) is set to five which covered most of the EEG rhythms and waveforms. Parameters derived from wavelet decomposition are: variance, skewness, fluctuation intensity of wavelet coefficients at 2–5 scales of detail and level 5 of approximation. In addition, time domain parameters such as average duration and amplitude of half-waves are obtained from signal epochs that are reconstructed from each of the five wavelet scales.

2.3.4 Complexity measures—This group include: fractal dimension of the waveform, spectral entropy, wavelet subband entropy and AR goodness of fit. It was reported (Esteller et al., 1999) that fractal dimension increases in the ictal period and can be used to detect a seizure onset. Entropy is used as a measure of “uncertainty” or the degree of randomness of the EEG epoch. We also used the residual power of the 2nd order AR model as a goodness of fit measure.

2.3.5 Preprocessing and feature subset selection—The features extracted from the EEG have values that lie within different dynamic ranges. Features with large values have a larger influence in the output than features with small values, out of proportion to their significance in the design of the classifier. The problem is overcome by normalizing the features so that their values lie within similar ranges. We used linear normalization via the respective estimates of the mean and variance.

Feature selection plays an important role in classification problems. To improve classification performance, a large size of feature vector is desirable, however this size can not be increased indefinitely, nor is it practical to run experiment on all possible features subsets. High dimensional classifiers have a greater ability to discriminate complex patterns at the cost of a greater potential to overfit. This is especially true for the case of small training sets.

Beside computational load and overfitting problems, irrelevant and redundant features can degrade the performance of the RNN. Irrelevant features can blur the boundaries between classes and increase overlap in a nonlinear manner. Redundant ones can also obstruct understanding how decisions have been made. To increase the classification accuracy, both irrelevant and redundant features have to be discarded. This involves the use of a feature selection algorithm.

Our approach utilizes the mutual information concept as the feature selection criterion. By definition, the mutual information is a measure of general interdependence between features (Duda et al., 2001). The algorithm of automatic feature selection is based on Battiti's (Battiti, 1994) Mutual Information Feature Selector (MIFS). The MIFS evaluates mutual information between individual features and outputs (class labels), and selects those features that have maximum mutual information with outputs and are less redundant.

This feature selection procedure is channel-specific and has been performed separately for each channel of the training data set. The final number of features used as inputs for RNN depends on the number of relevant features selected by the MIFS. This number may vary significantly with each patient because of different morphology of seizures. For example, if seizure onset patterns represent a prominent rhythmic activity in delta-theta range then the number of features selected by MIFS technique is usually reduced significantly, in some case up to 2 times. In other cases of the pre-onset patterns representing mixture of EMG, spikes and other EEG activity not clearly visible, the resulted feature subset is only slightly reduced (e.g., from 58 to 56).

2.4 RNN

Artificial Neural Networks (ANN) including Recurrent Neural Networks (RNN) are a powerful tool for pattern recognition problems. Unlike the traditional statistical classifiers, ANNs do not need any a priori hypothesis about data distributions since they provide their own model, formed in the training phase by learning from the examples of the training set.

The neural network implemented in our algorithm is a 3-layer RNN, completely interconnected, with the Levenberg-Marquardt learning algorithm. RNN have good convergence properties and can perform successful classification with relatively small amounts of training data. The temporal representation capabilities of the RNN networks can be significantly better than those of feed-forward multilayer perceptrons (MLPs), and unlike other networks, RNN are capable of representing and encoding strongly hidden states, i.e., states in which a network output depends on an arbitrary number of previous inputs. RNNs have been applied to epileptic seizure detection for patients with implanted electrodes (Petrosian et al., 1997, 2000; Bates et al., 2000, 2003).

In our algorithm, the RNN analyzes each channel independently. The number of inputs and the number of hidden layer nodes are determined by the size of the feature vector for each channel. The number of outputs is fixed and equal to five (background, pre-ictal, ictal and post-ictal patterns, artifacts). Our training data set was split into same 5 groups and each epoch in the training set has been labeled. Assigning five output categories rather than three (background, pre-ictal, ictal) makes the neural network much more robust.

Two of the RNN output nodes can be used for seizure warning purposes. The preictal node is used to recognizing preictal (pre-onset) patterns. The ictal node is used to recognizing early ictal (early onset) patterns.

One of the problems we addressed is the training of RNN on the small data set. A network with too many parameters can memorize all the training examples with the associated noise, errors and inconsistencies, and therefore perform a poor generalization on new data. This phenomenon is known as overfitting. Solutions to the overfitting problem include early stopping of training using a validation set and training with noise. When the training set is small, one can generate virtual or surrogate training patterns and use them as if they were normal training patterns sampled from the original seizure.

We allow a certain degree of memorization because we train the RNN to recognize seizures specific for the patient. Because of small training data set, additional surrogates for pre-ictal and ictal periods were generated. The surrogates were manufactured from the real seizures by randomizing the phase spectrum of the original seizure epoch and retaining the amplitude spectrum. Such surrogate data sets will preserve the autocorrelation properties of the original data set.

Typical network architecture used (inputs:hidden nodes:outputs): 30-30-5, 32-32-5, 36-36-5, 48-48-5 or 56-56-5. Each RNN (one per channel) is trained individually and its weights are saved in a file to be used during seizure recognition phase.

2.5 Combining

A final decision regarding the detection of pre-onset or onset pattern is made after combining individual RNN outputs in time and space. The detection event is declared if at least N channels have RNN output greater than the threshold in M consecutive epochs. This allows us to reject false channel-based detections and significantly reduce the false alarm rate. This is effective because the preictal and ictal patterns have a tendency to concentrate in time and space.

The optimal number of channels N and the number of consecutive epochs M for each patient is determined using all available data in the training and validation window. Training window is defined as a portion of study, e.g. day 1, which used to select training samples for RNNs. Each RNN was first trained to recognize training seizure samples and reject other non-seizure samples. The quality of RNN is validated on a validation period. The validation (or optimization) window is defined as a portion of study which is used to control the quality of RNN training and tune the space-time combining parameters.

Channels with poor performance during training and validation windows are excluded. The decision-making module performs an exhaustive search on all possible channel-epoch combinations and selects the combination that exhibits best performance in the training and validation periods combined. The optimization is done consecutively using sensitivity, false detection rate and minimal detection delay criteria. Preictal and ictal outputs are handled independently by the decision-making module to generate a pre-onset detection and an onset detection. This provides two opportunities to find a seizure warning solution in an individual subject.

2.6 Expert Input

Although our seizure pre-onset detection algorithm automatically selects features for each channel, and automatically forms decision-making logic, it still uses Expert input to select training samples and channels. The Expert selects the group of channels depending on the nature of each patient's seizure. If the nature of seizure is ambiguous then the Expert selects either all channels or several subsets of channels to provide coverage of possible centers of

focal seizure activity. In the case of generalized seizures any of one of these subsets can be used for seizure recognition.

Data from the training seizure(s), plus samples of background and artifact are selected by the Expert and presented to the RNN for training. The training seizure is divided into the following consecutive segments: near inter-ictal (approximately 2 minutes of continuous background EEG, immediately prior to the pre-ictal window), pre-ictal (up to 1 minute of continuous EEG immediately prior to seizure onset), ictal (up to 1–2 minutes continuous EEG immediately following seizure onset), post-ictal (up to 2 minutes continuous EEG immediately following the end of the ictal window). The Expert uses these approximate boundaries to score each channel separately. The actual duration of training samples varies and depends on the actual length of pre-ictal, ictal and post-ictal activity for each patient. For example, the ictal window starts with EEG onset and ends with the termination of seizure. In addition, the Expert reviews the interictal EEG to provide samples of awake, sleeping, movement, muscle, ocular, chewing, and 60 Hz activity.

Expert analysis is also used to judge the quality of RNN training and validation. Selected false alarms occurring in the training and validation periods are added to the training dataset, new feature vectors then extracted and RNN re-trained. The training is stopped when RNN reaches the lowest false alarm rate over both training and validation windows and when training seizure is detected. Candidate channels which failed during training (e.g., RNN convergence problems) are eliminated at this step.

3. Results

Results are presented from both pre-onset (trained on the pre-ictal EEG) and onset (trained on the ictal onset) detections. All seizures in this study were initially reviewed by at least two scorers to identify **Te** - the time of electrographic onset (**EO**) which is defined as the earliest evidence of ictal EEG that proceeds inexorably to the seizure (Geiger and Harner, 1978). The scorers were blinded to the results of automatic detections. The detector performance was assessed using standard measures:

- True positives (TP): the number of seizure detections that coincided with the Scorers.
- False positives (FP): the number of seizure detections that did not coincide with the Scorers.
- False negatives (FN): the number of seizures identified by the Scorers, but missed by the detector.
- Number of Seizures (NS): the number of seizures identified by the Scorers.
- Sensitivity of the detector: true positives/number of seizures $TP/NS \times 100$.
- False alarm (FA) rate: number of false detections per hour (or day) $FA=FP/T_s$, where T_s is the length of the study excluding training/optimization windows and the duration of the false positive clusters.
- Positive Predictive Value (PPV): true positives/all detections $TP/(TP+FP)$.

The performance of the detection algorithm was also evaluated by comparing the time of detection, **Td** with this human scored onset, **Te**: **Warning time = Td-Te**.

The seizure early detection algorithm was tested on long continuous recordings ranging from 15 to 62 hours. Each patient's recording was split into three separate, consecutive datasets: 1) the training set, 2) the validation (and optimization) set and 3) the testing set:

- The initial portion of each long term EEG recording, containing one or sometimes two seizures (see above) the training set, was used for feature selection and single-channel RNN training.
- The independent validation set was selected from the next portion of the EEG recording.
- The remaining EEG recording containing one or more seizures, the testing set, was used to evaluate the performance of previously trained and validated pre-onset/onset detectors. No data from the testing set were used for training or validation.

Based on distribution of pre-onset and onset patterns, we selected a 5-min time window as a measure of association with early seizure detection event, similar to the way the “prediction horizon” is defined by Litt et al. (2001) and Mormann et al. (2007). All pre-onset or onset detections made within 5 minutes of each other are clustered into a single seizure event.

3.1 Pre-onset and Onset Detections

Successful pre-onset detections were obtained in 14 patients. The remaining 11 patients were rejected during training or validation. They either did not generate reliable pre-onset detections in the training/validation window or RNN training could not be completed because lack of convergence. Visual EEG features of the preictal window were minimal to absent. Even so, pre-onset detection with very low false-positive rate was possible in 14 of 25 patients. The inability of RNN to find consistent patterns of EEG/EMG activity in the pre-ictal window in the others may be due simply to the fact that none were present.

Onset detection was successful in all 25 patients, not surprising in view of evident EEG/EMG ictal onset features in all. Table 2 summarizes the test results. Table 3 gives patient-by-patient results.

The results can be summarized as follows:

- Onset detection was successful in all patients (all 46 test seizures detected, 100% sensitivity),
- Pre-onset detection was successful in 14 patients (all 28 test seizures from these patients were detected, 100% sensitivity).
- 72% of seizures (17 patients) were detected before EEG onset.
- False detection rate averaged 0.06/hour for pre-onset detection and 0.023/h for onset detection.
- False detections were less than 2/day in 71% of patients for Pre-onset detection and in 92% of patients for Onset detection.
- Pre-onset detection had PPV of 0.5 or more in 9 Patients and 4 had a perfect PPV of 1.0.
- Onset detection had PPV of 0.5 or more in 22 Patients and 15 had a PPV of 1.0, indicating 100% accuracy.

Figure 2 shows a distribution of **Td**. For patients, where pre-onset detection was reliable the corresponding early onset detection times are not plotted. Detections later than -5 s are primarily from the early onset detector. Three modes are suggested. The mode at zero latency is dominated by 9 seizures from three CPS+G patients (plus 6 seizures from CPS patients). This is consistent with the idea that more and faster propagation is associated with less warning time. There is a group of seizure concentrated in the region of 40–60 sec before EEG onset, EO. This group is entirely composed of seizures from 17 CPS patients. Finally there are 7

seizures reliably detected more than 150 sec before EO. Review of these outliers shows that there is similar continuing activity in these time periods that “should” be detected based upon our training data. For example, in Patient 20, test (seizure 36 and 37), the algorithm detected pre-onset patterns at 16 and 19 minutes before EEG onset. In this patient, the pre-onset patterns represented continuing activity which lasted up to EEG onset. In another case (Patient 12, seizure 24), the pre-onset patterns were detected early (−181 seconds). In this case, there was muted rhythmic activity in the preictal window that previewed the seizure onset. This activity also occurred elsewhere, creating 2 false alarms. The underlying pathophysiological mechanisms are obscure. Abortive subclinical seizure activity is just one possibility.

Onset detector in Patient 25 has been optimized to have 0 false alarm rate which significantly reduced the warning time to +51 s after EEG onset. In this case, the EEG onset has been highly contaminated by muscle activity in all channels which prevented early detection of seizure. Note, however that pre-onset detection for this patient was effective.

Some patients whose detections occur at EEG onset may still retain voluntary ability and thus be considered as receiving useful warnings. This includes 88% of all patients analyzed. Indeed, Block and Fisher (1999), reported voluntary signaling of seizure onset by 44% of 77 patients with complex partial seizures at about the time of seizure onset in scalp EEG (with considerable variability).

3.2 Case Study 1

Case study 1 is from Patient 1 and is a demonstration example illustrating the detailed functioning of pre-onset detection. Figure 3 is an 8 minute view around testing seizure #1. At this scale, the RNN outputs can be seen for each 2.56 second epoch and can be related to the EEG in the upper part of the illustration. The three lowest traces are the RNN outputs for three EEG channels. The ordinates are CR, certainty of recognition, scaled from 0–1 with a detection threshold at 0.9 illustrated. Time zero is the electrographic onset time (EO) as scored by two expert reviewers. The trace labeled “Detector Output” is the output of the decision matrix, either 0 or 1 depending on whether the decision matrix criterion is met, for example: “three consecutive detections simultaneously in three channels”. In this case, at time −48 seconds to time zero, there is a string of epochs in each individual channel that exceed threshold resulting in a string of about 17 positive decision matrix outputs. This represents a very strong (reliable) pre-onset detection with a warning time of over 40 seconds before EO. Note also there are several consecutive epochs in channel T4–T6 at −240 seconds where threshold is exceeded, but this does not occur simultaneously in the other channels, hence no detection. This situation occurs commonly throughout the recording and is the mechanism by which false positives are avoided. Referring to figure 4, for the same recording all 24 hours are displayed. In this case, due to the highly compressed time scale, each dot is about 180 seconds wide, so many are superimposed. It can be seen that there are many cases of exceeding threshold in individual channels, but it turns out that the decision matrix criterion is met only at times in the immediate vicinity of seizures, resulting in the pre-onset detection of all test seizures and a zero false alarm rate.

3.3 Case study 2

Patient 2 was recorded with a combination of scalp and intracranial electrodes. Although we did not analyze the intracranial EEG with our method, it is interesting to look at our results with respect to the full recording.

Figure 5 shows 128 sec of combined recording from deep intracranial electrodes (26 channels) and scalp (last 6 channels) during a stereotypic complex partial seizure of temporal lobe origin. The seizure begins with rhythmic and irregular muscle and movement activity in temporal

scalp electrodes (A) at a time when no change in intracranial or extracranial EEG is present. Over the next 10–15 seconds independent spikes subside bilaterally (B) and there is amplitude reduction in intracranial channels. Finally, a full 30 sec after the onset of chewing artifact and 15 sec after widespread EEG attenuation, exquisitely localized fast rhythmic ictal onset (C) is noted in a single right temporal depth electrode. Rhythmic scalp activity follows in 8 sec (D).

We see the inexorable progress from scalp muscle activity to general EEG attenuation well before the intracranial rhythmic ictal activity that is often taken as the best indicator of seizure onset. While this raises important questions about the mechanism of seizure initiation and the possibility of ictal onset in a site distant from those chosen for electrode implantation in this case, we emphasize the useful warning information that can be obtained from analysis of stereotypic early ictal muscle activity, in concert with analyzed EEG features in scalp electrodes using RNN. In this case RNN pre-onset detection, training only on scalp activity, occurred at A.

4. Discussion

4.1 Source of pre-onset detections

Now that we can detect seizures from scalp EEG recording prior to EEG onset in selected patients the question arises, what are we detecting? At present, we can only speculate. The first possibility is that ictal activity deep in the brain is expressed as a change in preictal background EEG, incidence of paroxysmal activity, and/or non-EEG activity such as muscle. We have been unable to visually identify EEG changes uniquely associated with pre-onset detections in majority of subjects. In case study 1, a stereotypic muscle artifact was present in each preictal window that may have been unique, that is, not appearing anywhere else in the background scalp EEG. A second possibility is more problematic, i.e., the possibility of a pre-seizure brain state that is regularly associated with the seizure itself. But if it is regularly associated, why not just say it an early part of the seizure? After all a seizure is already an ordered sequence of events, not just a single event. Our present concept of when a seizure begins is highly pragmatic; it begins when we can see it, either in the EEG or in behavior. Perhaps we should replace the concept of seizure with that of **seizure cascade**, somewhat analogous the cascade of events now well-known to take place in diverse physiological processes, such as blood coagulation or DNA incorporation, and allow for a series of states, of varying duration, some without obvious visual electrographic features, even with deep brain recording.

The changes in EEG “energy” reported by Litt et al. (2001) are likely to represent longterm modulation of the epileptogenic focus, for example by ultradian neurohumoral rhythms. More local, more immediate changes in EEG or other measures of brain are more like to relate to the nascent ictal onset. Interestingly, the work of Federico et al. (2005) suggests that pre-ictal brain activity just a few minutes before seizure onset need not be at the site of presumed epileptogenesis, but contralateral or hemispheric. This suggests the possibility of preictal mechanisms involving multiple sites and possible interaction among sites as additional preictal mechanisms. Clearly we are just beginning to learn about the preictal state.

4.2 Samples of EEG readings showing true positive and false positive detections

Figures 6–11 are 20-sec print screens of pre-onset patterns. Horizontal bar corresponds to the section of EEG where pre-onset detection events were declared, the triangles indicate EEG channels analyzed for the specific patient. The expert scored EEG onset is not on the 20-sec page illustrated. Although in many cases, the pre-onset patterns were not clearly identifiable by the human expert, there were a variety of pre-onset patterns in our study including spikes, EMG activity, sharp waves, delta increase, eye movements etc. Figures 7(A,B), 8(A,B) and 11

(A,B) present the samples of true positive pre-onset detections as well as the samples of false positive detections.

Recognizing characteristic patterns during periods preceding seizures is only half of the pattern recognition challenge. The algorithm must also reject similar patterns in the remaining 24+ hours.

4.2 Applications

The developed seizure pre-onset/onset detection algorithm has a potential for deployment in current or emerging real-time applications in patients with medically intractable epilepsy, including demanding uses such as (1) the triggering of radionuclide injection for the acquisition of SPECT scans for seizure localization, (2) gating the delivery of timely electrical stimulation, drug delivery or cooling for seizure treatment, (3) alerting the staff of an epilepsy center to an anticipated seizure, and (4) providing the basis for a device that could be worn by a patient to alert to an impending seizure in time to take precautions.

4.3 Comparison with other detectors

Table 4 summarizes the performance of our Pre-onset and Onset detectors compared to the published results for other experimental “early onset” detection systems. Note, that Osorio et al. and D’Alessandro et al. used intracranial EEG recordings.

The results from D’Alessandro et al. (2003) are included, because the work was focused on a 10-minute period prior to the seizure. We did not compare to extremely long term prediction algorithms such as Litt and Echauz (2002), Iasemidis et al. (2003), Hively et al. (2003), Le Van Quen et al. (2003), most of which used intracranial EEG.

To put our results in context with previously reported results, several teams have reported on early onset detection based on analysis of scalp EEG. The best results were attained with patient-specific algorithms. Our results are similar to the best previously reported, those of Gotman and Qu (1997), and support the conclusion that patient-specific algorithms using scalp EEG can be very reliable for early onset detection for patients in epilepsy monitoring units.

The unique result being reported here is that, for about half of these patients, using our same patient-specific techniques on scalp EEG, pre-onset detection can be made similarly reliable, providing a longer warning time prior to seizure onset.

4.4 Future work

The following areas of future work have been identified:

- **Training automation.** Selection of training samples, training of individual RNNs and tuning the decision making module currently require a substantial amount of expert input and supervision, particularly for pre-onset detection. One of the future tasks will be to develop automatic procedures and software to perform effective training with a minimum human input.
- **Combining with generic seizure detection.** The proposed detector has been trained on first one or two seizures in order to detect subsequent similar seizures in same patient. The detector exhibited very good performance when testing seizures had pre-ictal and ictal patterns similar to the training seizure. If there are several types of seizure in same patient then the detector will likely detect only seizures similar to a training template. In this case, coupling the proposed algorithm with generic seizure detector may improve overall system utility.

- **Performance improvement.** Our patient database had only a limited number of seizures per patient, usually two or three. We think that increasing the number of training seizures will improve the overall system performance.
- **Validation for clinical use.** Our algorithm was mostly tested on 24-hour long studies. We are planning to conduct validation of the proposed algorithm on longer, multi-day studies including those which have a gap between training and testing recordings.

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Appendix A: Spectral, Wavelet, Time-Domain and Complexity Features

The following parameters were computed and included in the feature library.

Spectral (FFT) parameters

- Relative power in delta (0–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), sigma (12–16 Hz), beta1 (16–20 Hz), beta2 (20–24 Hz), beta3 (24–28 Hz) and beta4 (28–32 Hz) and in the high frequency band (32–70 Hz)

$$P = \sum_{f_i \in \Delta F} S(f_i)$$

where, $S(f)$ is the power spectrum of EEG epoch, ΔF is the frequency band of interest.

- Mean frequency of EEG spectrum

$$f_m = \frac{\sum_{f_i \in \Delta F} S(f_i) f_i}{\sum_{f_i \in \Delta F} S(f_i)}$$

- Dominant or peak frequency. It is defined as the frequency of the dominant (maximal) peak in a spectrum

$$f_d = \arg \max_{\Delta F} \{S(f)\}$$

- Width of the dominant spectral peak. It is defined as the difference between the frequency corresponding to half the amplitude of the dominant peak in its falling slope and the frequency corresponding to half of this amplitude in the rising slope.

Wavelet processing parameters

Detail wavelet coefficients W_i^j for 2,3,4,5 levels of decomposition and approximate coefficients for level 4 have been used to compute these parameters:

- Mean M_j of wavelet coefficients

$$M_j = \frac{1}{N_j} \sum_{i=1}^{N_j} W_i^j$$

where j is the level of decomposition, N_j is the number of wavelet coefficients at level j .

- Variance V_j of wavelet coefficients

$$V_j = \frac{1}{N_j} \sum_{i=1}^{N_j} [W_i^j - M_j]^2$$

- Skewness S_j of wavelet coefficients

$$S_j = \frac{\frac{1}{N_j} \sum_{i=1}^{N_j} [W_i^j - M_j]^3}{\sqrt{V_j^3}}$$

- Fluctuation Intensity of wavelet coefficients

$$FI_j = \frac{1}{N_j} \sum_{i=1}^{N_j} \frac{\sqrt{\langle [W_i^j]^4 \rangle - \langle [W_i^j]^2 \rangle^2}}{\langle [W_i^j]^2 \rangle}$$

Time-Domain parameters

- Average duration of half-waves $\bar{D}$
- Average amplitude of half-waves $\bar{A}$
- Coefficient of variation of half-wave duration D

$$CV_D = \frac{\sqrt{\frac{1}{N} \sum_i [D_i - \bar{D}]^2}}{\bar{D}}$$

- Coefficient of variation of half-wave amplitude A

$$CV_A = \frac{\sqrt{\frac{1}{N} \sum_i [A_i - \bar{A}]^2}}{\bar{A}}$$

- Average nonlinear energy of the epoch $E[NLEO(n)]$

$$NLEO(n) = X^2(n) - X(n+1)X(n-1)$$

where $X(n-1)$, $X(n)$, $X(n+1)$ – EEG samples at times $n-1$, n and $n+1$.

Complexity parameters

- Goodness of fit. For the second order AR model, residual errors $e(n)$ can be calculated as follows

$$e(n) = \sum_{m=0}^2 a(m)X(n-m)$$

where $a(m)$ are AR coefficients and $a(0)=1$. Burg's algorithm is used (Burg, 1967) to get the estimates of AR coefficients and the residual errors. The goodness of fit is estimated as $\sigma^2 = E[e(n)e(k)]$.

- Spectral entropy

$$SE = - \sum_{f_i \in \Delta F} S(f_i) \log S(f_i)$$

- Wavelet entropy

$$WE_j = - \frac{1}{\log N_j} \sum_{i=1}^{N_j} P_j(i) \log P_j(i),$$

$$P_j(i) = \frac{(w_i^j)^2}{\sum_{k=1}^{N_j} (w_k^j)^2}$$

where P_j - squared and normalized wavelet coefficients at level j , N_j is the number of wavelet coefficients at level j .

- Fractal dimension of the epoch (Petrosian, 1995)

$$FD = \frac{\lg N}{\lg N + \lg \left(\frac{N}{N+0.45} \right)}$$

Where N is the epoch length, S is the number of sign changes.

Appendix B: Normalization of Training Data

One of the most common forms of normalization consists of a simple linear rescaling of the features. This is often useful if different elements of input feature vector have typical values which differ significantly. Denote the training data set as matrix $\mathbf{P}$ of dimension N (number of feature vectors) by M (number of elements (features) in vector):

$$\mathbf{P} = \begin{bmatrix} p_{11} & p_{12} & p_{1N} \\ p_{21} & p_{22} & p_{2N} \\ p_{M1} & p_{M2} & p_{MN} \end{bmatrix}$$

Matrix $\mathbf{P}$ needs to be normalized so that inputs of RNN will have zero mean and unity standard deviation over the transformed training set. By applying a linear transformation we can arrange for all of the RNN inputs to have similar values:

$$\bar{p}_m = \frac{1}{N} \sum_{n=1}^N p_{mn}, \quad \sigma_m^2 = \frac{1}{N-1} \sum_{n=1}^N (p_{mn} - \bar{p}_m)^2.$$

$$\tilde{p}_{mn} = \frac{p_{mn} - \bar{p}_m}{\sigma_m}$$

where $\bar{p}_m, \sigma_m$ are mean and standard deviation of each feature with respect to the training data set, and $\tilde{p}_{mn}$ is the re-scaled or normalized feature.

FIG 1.
Early seizure detection algorithm

FIG 2.
Distribution of 46 (test seizures only) seizure detection times from 25 patients.

FIG 3.
8-min EEG (top graph) and decision-making module output with individual channel RNN outputs (bottom graph).

FIG 4.
Detection summary, individual channel RNN outputs and decision matrix output showing 100% sensitivity and 0 false alarm rate.

FIG 5. Patient 2 (combination scalp, last six channels, and intracranial recording). A: Muscle & movement in temporal scalp electrodes. B: Amplitude reduction. C: Rhythmic ictal onset in right temporal intracranial electrode. D: Rhythmic activity in scalp electrodes.

FIG 6.
Mixture of EEG, EMG and Eye movements. Triangles indicate EEG channels processed, horizontal bar corresponds to the section of EEG where pre-onset detections occurred.

FIG 7. (A, B). Poly-spike bursts, eye movement, left temporal muscle activity. A - true positives pre-onset detections, B - false positives. Triangles indicate EEG channels processed, horizontal bar corresponds to the section of EEG where pre-onset detections occurred.

Figure 8.

(A,B). Bifrontal sharp and slow(delta) activity. A - true positive pre-onset detections, B - false positives Triangles indicate EEG channels processed, horizontal bar corresponds to the section of EEG where pre-onset detections occurred.

FIG 9.

Bilateral spikes and slight increase in delta. Triangles indicate EEG channels processed, horizontal bar corresponds to the section of EEG where pre-onset detections occurred.

FIG 10. Left temporal muscle activity. Triangles indicate EEG channels processed, horizontal bar corresponds to the section of EEG where pre-onset detections occurred.

FIG 11.
 (A,B). Spike and delta activity. A - true positive pre-onset detections, B - false positives.
 Triangles indicate EEG channels processed, horizontal bar corresponds to the section of EEG
 where pre-onset detections occurred.

Table 1

Number of training, validation and testing seizures per patient

Patient#	Total seizures	Training seizures	Validation seizures	Testing Seizures
1	5	1	0	4
2	5	1	0	4
3	3	1	1	1
4	5	2	1	2
5	2	1	0	1
6	3	1	1	1
7	2	1	0	1
8	2	1	0	1
9	7	1	0	6
10	5	2	1	2
11	2	n/a	n/a	n/a
12	3	1	1	1
13	2	1	0	1
14	2	1	0	1
15	2	1	0	1
16	6	2	1	3
17	3	1	1	1
18	3	1	0	2
19	4	1	1	2
20	7	2	1	4
21	3	1	0	2
22	3	1	1	1
23	2	1	0	1
24	2	1	0	1
25	3	1	1	1
26	2	1	0	1

TABLE 2

Summary of test results

	Preonset detector*	Onset detector
Number of Test Seizures (NS)	28	46
True Positives (TP)	28	46
False Negatives (FN)	0	0
Sensitivity (TP/NS*100)	100%	100%
False Positives, FP (FP/hour)	24 (0.06/h)	20 (0.023/h)
Pos. Pred. Value (PPV)	0.54	0.70
Warning time (Td-Te)	Median: -51 seconds Range: -1140 to -16 seconds	Median: +4 seconds Range: -12 to +51 seconds

* Preonset detector results are based on 14 patients.

TABLE 3

Patient-by-Patient Summary

Patient	Study Duration, (hrs)	Sz #, (type)	Earliest Detection Time, (s) Preonset/Onset Detectors	FP N, Preonset/Onset detectors	FA Rate N/h, Preonset/Onset detectors	ppv, Preonset/Onset detectors
Pt 1	24	1 (cps) 2 (cps) 3 (cps) 4 (cps)	-41/+5 -92/+6 -87/+8 -89/0	0/0	0/0	1.0/1.0
Pt 2	30	5 (cps) 6 (cps) 7 (cps+g) 8 (cps)	-33/-2 -38/-12 -41/-1 -35/+5	0/0	0/0	1.0/1.0
Pt 3	15	9 (cps)	-33/-1	3/0	0.2/0	.25/1.0
Pt 4	24	10 (cps) 11 (cps)	-48/10 -31/-1	0/0	0/0	1.0/1.0
Pt 5	26.5	12 (cps)	NA/-5	NA/1	NA/0.04	NA/.50
Pt 6	24.3	13 (cps)	-48/+10	0/0	0/0	1.0/1.0
Pt 7	24.5	14 (cps+g)	NA/+3	NA/0	NA/0	NA/1.0
Pt 8	24	15 (cps)	NA/+8	NA/1	NA/0.04	NA/.50
Pt 9	27.5	16 (cps) 17 (cps+g) 18 (cps+g) 19 (cps+g) 20 (cps) 21 (cps)	NA/0 NA/-3 NA/+5 NA/+7 NA/+12 NA/+15	NA/1 NA/0	NA/0.04 NA/0.04	NA/.86
Pt 10	24.3	22 (cps) 23 (cps)	-69/+4 -48/+7	3/0	0.12/0	0.40/1.0
Pt 11	4.9	-	-/-	-	-	-
Pt 12	24	24 (cps)	-181/+11	2/0	0.08/0	.33/1.0
Pt 13	24	25 (cps+g)	NA/-1	NA/0	NA/0	NA/1.0
Pt 14	34.4	26 (cps+g)	NA/-5	NA/0	NA/0	NA/1.0
Pt 15	45.9	27 (cps+g)	-174/-10	0/0	0/0	NA/1.0
Pt 16	21.3	28 (cps) 29 (cps) 30 (cps)	-25/+6 -51/+7 -42/+7	1/1	0.05/0.05	.75/.75
Pt 17	23.75	31 (cps)	-16/+1	1/1	0.04/0.05	.5/.5
Pt 18	55	32 (cps) 33 (cps)	NA/+4 NA/+4	NA/5	NA/0.09	NA/.29
Pt 19	43.5	34 (cps)	-51/+3 -61/+2	2/2	0.04/0.04	.50/.50

Patient	Study Duration, (hrs)	Sz #, (type)	Earliest Detection Time, (s) Preonset/Onset Detectors	FP N, Preonset/Onset detectors	FA Rate N/h, Preonset/Onset detectors	PPV, Preonset/Onset detectors
Pt20	41	35 (cps)	-960/+4 -1140/+3 -193/+3 -191/+5	4/5	0.1/0.12	.50/0.44
Pt21	62	40 (cps+g) 41 (cps+g)	NA/+1 NA/-1	NA/0	NA/0	NA/1.0
Pt22	25	42 (cps)	-204/+7	2/1	0.08/0.04	.33/.50
Pt23	47.5	43 (cps)	NA/+25	NA/0	NA/0	NA/1.0
Pt24	32	44 (cps)	NA/+1	NA/2	NA/0.06	NA/.33
Pt25	47.25	45 (cps)	-100/+51	6/0	0.12/0	.17/1.0
Pt26	23.75	46 (cps)	NA/+7	NA/0	NA/0	NA/1.0

TABLE 4

Comparison of seizure pre-onset/onset detectors

	Type of Detector	Patient/Seizure Database	Sensitivity, %	False Alarm Rate	Earliest Detection ^{**} : Avg & (Range)
D'Allesandro et al. (2003)	Prediction	4 patients Intracranial	62.5%	0.28/hour	-207 seconds (-333.6 to -108.6)
Osorio et al. (2002)	Early Onset (generic with adaptation)	14 patients Intracranial 34 seizures	100%	0.05/hour	+4.8 seconds [*] (-6.8 to +7.1)
Gotman and Qu (1997)	Early Onset (patient specific)	12 patients Scalp 47 seizures	100%	0.02/hour	+9.3 seconds (+3 to +15.6)
Shoeb et al (2004)	Early Onset (patient specific)	36 patients Scalp 139 seizures	94%	0.25/hour	+8 seconds (+4.8 to +11.2)
Grewal and Gotman (2005)	Early Onset (generic with tuning)	19 patients Intracranial 100 seizures	89.4%	0.22/hour	+17.1 seconds
Saab and Gotman (2005)	Early Onset (generic with tuning)	16 patients Scalp 69 seizures	77.9%	0.86/hour	+9.8 seconds
Wilson (2005)	Seizure Detection (patient specific)	10 patients Scalp 57 seizures	89%	0.56/h	Not reported
Meier et al (2008)	Early Onset (generic)	57 patients Scalp 91 seizures	96%	0.25-0.5/h	+1.6 seconds (-4 to +10)
Onset Detection	Early Onset (patient specific)	25 patients (Scalp/EKG) 46 seizures	100%	0.02/hour	+4 seconds [*] (-12 to +51)
Preonset Detection	Short Term Prediction (patient specific)	14 patients (Scalp/EKG) 28 seizures	100%	0.06/hour	-51 seconds [*] (-1140 to -16)

* Median

^{**} The earliest detection time with respect to the human-scored EEG onset (Te). - precedes Te, + follows Te.