SEIZURE WARNING SYSTEM AND DYNAMIC RESPONSE TO ELECTRICAL STIMULATION IN A RODENT MODEL OF CHRONIC LIMBIC EPILEPSY

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Abstract: This study investigates seizure prediction performance and EEG dynamical response to electrical stimulation in an animal model that mimics human mesial temporal lobe epilepsy (MTLE). We performed an automated seizure warning algorithm (ASWA) on long-term continuous EEG recordings obtained from five freely moving rats with chronic limbic epilepsy (CLE). This algorithm is based on the detection of convergence of short-term maximum Lyapunov exponents (STLmax) among brain regions. The performance was evaluated with different warning horizons (WH) and was compared with those obtained from statistically derived naïve seizure warning schemes. The results demonstrate that ASWA performs significantly better than naïve warning schemes ($p<0.01$). We also investigated the responses of EEG dynamics to electrical stimulation in CLE rats. A single stimulas was delivered to hippocampus short after a seizure warning was issued by ASWA. Preliminary results suggest that the mechanism underlying the anticonvulsant effect of hippocampal stimulation may involve dynamical resetting. The ability to warn of impending seizures and intervene to modify the brain dynamics in this model provides an opportunity to develop and test novel closed-loop intervention techniques directed toward the prevention of impending seizures.

Keywords—**automated seizure warning, chronic limbic epilepsy model, hippocampal stimulation**

Introduction

The epilepsies are a family of neurological disorders characterized by seizures which are transient, recurrent perturbations of normal brain function. As a chronic condition, epilepsy affects about 1% of the population in the United States [1]. Methods derived from the patterns of quantitative dynamical descriptors of electroencephalographic (EEG) signals have been used to demonstrate the existence of preictal transition in human temporal lobe epilepsy (TLE) [2-7]. Based on the detection of STLmax convergence among recording electrode sites before a seizure, we have developed several algorithms designed to monitor the spatiotemporal dynamics of the EEG signals and predict seizures [8-10]. Preliminary analyses of these algorithms indicate that they can predict seizures with at least 80% sensitivity and a false-prediction rate of approximately 0.125 per hour. The present study evaluates the application of an ASWA to a CLE rodent model. This seizure model is created by inducing prolonged seizures (status epilepticus) using electrical stimulation of the hippocampus [11]. After a period of several weeks to a month of recovery from the stimulation, the animals begin to have spontaneous seizures that continue for the rest of their lives [12]. This model has many of the features associated with human TLE including (1) similar electrophysiological correlates, (2) etiology, (3) pathological changes in the limbic system, and (4) seizure induced behavioral manifestations. In addition to these aforementioned characteristics, recent work suggests that this model shares many spatiotemporal characteristics of the EEG with human epilepsy [13-14]. These studies have reported preictal transitions that are similar to those observed in patients with epilepsy.

The ultimate goal of this study was to use this animal model to investigate closed-loop control schemes that would apply a therapeutic intervention when a seizure is likely to happen. In the current study, we first investigated the seizure predictability in the CLE model by employing an ASWA that has been tested in human EEGs. We tested the hypothesis that the performance of ASWA in CLE rats is better than naïve warning schemes (periodic and random warning). By performing ASWA on-line in real-time, we further studied the responses of EEG dynamics to

electrical stimulation delivered to hippocampus when a seizure warning was issued. Results of these investigation could form a basis for the design of closed-loop control schemes that would apply a therapeutic intervention when a seizure is likely to happen.

Materials and Methods

A. Animal Preparation and EEG Acquisition

Experiments were performed on two month old (250 g) adult male Harlan Sprague Dawley rats (n=5) weighing 210-265 g. Four 0.8 mm stainless steel screws (small parts) were placed in the skull to anchor the acrylic headset. Two were located 2 mm rostral to bregma and 2 mm laterally to either side of the midline. One was 3 mm caudal to bregma and 2 mm lateral to the midline. One of these served as a screw ground electrode. The last, which served as a screw reference electrode, was located 2 mm caudal to lambda and 2 mm to the right of midline. Holes were drilled to permit insertion of 2 stainless steel bipolar twist electrodes (1 mm tip separation) into the left and right ventral hippocampii for electrical stimulation and recording, and 2 stainless steel monopolar recording electrodes in the bilateral frontal cortical hemispheres. Rats were allowed to recover for a week after surgery before further procedures were performed.

The rats were electrically stimulated to induce seizures 1 week after surgery. The stimulation target was chosen by the technician based on behavioral response to stimulation and EEG afterdischarge patterns. Approximately 20-30 minutes after the stimulation, convulsive seizures (up to 1 min duration) were usually observed about every 10 min. At the end of the stimulus period, the EEG trace was observed for evidence of slow waves in all 4 monopolar traces. If this was not the case, the stimulus was re-applied for 10 minute intervals on another 1-3 occasions until continual slow waves appeared after the stimulus was terminated. Only rats that were responsive to stimulation and went on to develop spontaneous seizures were included in the study.

With successful seizure induction, the EEG continued to demonstrate < 5 Hz activity for 12-24 hrs and intermittent and spontaneous electrographic seizures (30 seconds - 1 minute in duration) for 2-4 hrs following an electrical stimulation session. Rats were observed for 12-24 hrs after stimulation for seizure activity, and food and water intake was monitored closely. Once their behavior stabilized, they were returned to their home room for 6 weeks while spontaneous seizures developed.

Each animal was connected through a 6-channel commutator and shielded cable to the EEG recording system, which consists of an analog amplifier (Grass Telefactor-Model 10), a 12 bit A/D converter (National Instruments, Inc), and recording software (HARMONIE 5.2, Stellate Inc. Montreal), which was synchronized to a video unit for time-locked monitoring of behavioral changes. A detailed description of the recording setup used in this study can be found in [12]. Each channel was sampled at a uniform rate of 200 Hz and filtered using analog high and low pass filters at cutoff frequencies of 0.1 Hz and 70 Hz, respectively. The recording system used a 4 channel referential montage and was set to a continuous mode so that prolonged data sets containing ictal as well as interictal data could be collected for analysis. EEG dataset pre-processing included removal of baseline wander using a Butterworth filter.

B. Description of Datasets

Long term continuous EEG recordings from 5 CLE rats with a total of 48 spontaneous seizures were included in this study. We selected these rats based on duration of recordings (at least two weeks), and number of seizures (at least 5 seizures). The mean total duration of recordings was approximately 19 days and the mean seizure interval was a little over 2 days (~ 49.7 hours). A summary of the test dataset is given in Table 1. Seizures were identified by review of technician logs, visual scanning of the recordings, and automated seizure detection algorithms. The seizures were confirmed and classified by a board-certified electroencephalographer who also made an independent determination of the time and anatomical location of electrographic seizure onsets.

Table 1: Summary of EEG datasets

Rat	Duration of EEG recordings (days)	Number of seizures	Range of Inter-seizure interval (hours)	Mean Inter-seizure interval (hours)
R-1	14.3	7	3.54 ~ 115.6	52.3
R-2	31.3	8	20.56 ~ 217.7	98.46
R-3	15.7	10	2.82 ~ 74.3	30.23
R-4	14.6	8	12.44 ~ 76.25	43.53
R-5	19.1	15	2.98 ~ 186.37	23.77
Total	**95.0**	**48**	**2.82 ~ 217.70**	**49.7**

C. Automated Seizure Warning Algorithm (ASWA)

Based on the spatiotemporal dynamics of EEG signals, ASWA involves the following steps:
(1) Calculate STLmax: As EEG signals are collected, a STLmax estimation is performed every 10.24 second window in each channel, creating a new time series of STLmax profiles with a 10.24 sec time resolution. STLmax quantifies the observed local chaoticity of a dynamical system, and is closely related to the average rate at which information is produced or destroyed. The rationale for the use of STLmax is based on the hypothesis that the epileptic brain progresses into and out of order-disorder states according to the theory of phase transitions of nonlinear dynamical systems [15]. Detailed descriptions of the method for calculating STLmax from nonstationary signals have been published previously [16].

(2) Select most critical channel groups: Based on the STLmax time profiles from all recording channels before and after the first available seizure, ASWA selects the most critical groups of EEG channels for prospective monitoring. The channel selection is performed automatically, based on a similarity index of STLmax profiles called T-index (derived from the paired T-statistic). The critical groups of electrode channels are defined as the channel groups that maximize the quantity $T(postictal) - T(preictal)$, where T(postictal) is the average T-index in the 10 minute window following the offset of the first seizure and T(preictal) is from the 10 minute window preceding the first onset. The selection of 10-minute intervals before and after the seizure in this process was based on our previous studies on dynamical resetting of epileptic seizures [17]. The average T-index values of these groups are monitored forward in time (moving window of 10.24 seconds at a time), generating T-index curves over time.

(3) Detect convergence of STLmax – Entrainment transition: An entrainment transition is detected when the average T-index curve for any of the critical groups falls below a dynamically adapted critical threshold. The adaptive threshold includes a "dead-zone" with an upper threshold UT and a lower threshold LT. An entrainment transition is detected if an average T-index curve is initially above UT and then gradually (at least 30 minutes of traveling time) drops below LT. Once an entrainment transition is detected, the algorithm will search for a new UT to be used for detection of the next transition.

(4) Issue a warning: After an entrainment transition is detected, the algorithm will determine whether a seizure warning should be issued. In this algorithm, if a transition is detected within the warning horizon from the previous warning, the transition is considered as part of a cluster of transitions and a new warning is not issued. Thus, a seizure warning defines mathematically the beginning of a new dynamical EEG state called the preictal transition.

D. Statistical Evaluation of Seizure Predictability

In this study, we compared the performance of the ASWA with statistically based seizure warning schemes that do not utilize information from the EEG signals (naïve seizure warning schemes). We utilized a periodic and a random prediction scheme [18]. The periodic and random prediction schemes are simple and intuitive. The periodic scheme issues a warning with a fixed time interval. The random scheme warns of an impending event with a random interval that follows an exponential distribution with a fixed mean.

For each of the test warning algorithms (ASWA, periodic and random), we evaluated seizure predictability using six different warning horizons (WH = 1 ~ 6 hours), defined as the period following a warning, during which a seizure is expected to occur. After the issue of a warning, it is considered as correct if the event occurs within the WH. If no event occurs within the window of the WH, the warning is classified as a false warning. The merit of a prediction scheme for a given prediction parameter is then evaluated by its probability of correctly predicting the next event (sensitivity) and its false warning rate (FWR) (specificity). The unit of FPR used here is per hour and thus FWR is estimated as the total number of false predictions divided by total number of hours of EEG analyzed. An ideal warning scheme should have sensitivity 1, and FWR 0.

The next step is to estimate the warning receiver operating characteristic (WROC) curve. The parameter used for the construction of each WROC curve were: the distance D between UT and LT (ASWA scheme), the interval T (periodic scheme), and the mean of the underlying exponential distribution λ (random scheme). For each warning algorithm, the sensitivity and FWR decreased when the value of its corresponding parameter increased, as expected. For the random scheme, since it essentially is a random process, each point in WROC curve (i.e., for each value of λ) was estimated as the mean sensitivity and mean FWR from 100 Monte Carlo simulations.

In some cases, the WROC curve may not be smooth and the superiority of one warning scheme over the other is difficult to establish. Usually, WROC curves are globally summarized by one value, called the area above (or under) the curve. Since the horizontal axis FWR of a WROC curve is not bounded, the area above the curve (AAC), given by

$$AAC = \int_0^{\infty} [1 - f(x)]\, dx \qquad (1)$$

is the most appropriate measure, where y = f(x), with x and y being the FWR and sensitivity respectively. Smaller AAC indicates better seizure warning performance. In this seizure warning application, since it is less important to evaluate the performance when sensitivity is low, we have estimated AAC with seizure warning sensitivity at least 50%.

E. Responses of EEG Dynamics to Electrical Stimulation

For this study, each rat first underwent a procedure for determining its afterdischarge (AD) threshold. Biphasic square wave pulse trains (AM Systems Inc.) were delivered using bipolar electrodes in the hippocampus. With the following stimulation parameters constant, (1) frequency = 125 Hz, (2) train duration =10 seconds, and (3) pulse width = 400 μseconds, the output current intensity was increased from an initial low value in small increments (10 ~ 20 μA) until ADs were observed in the simultaneously recorded EEG.

The study was conducted during the interictal state to study the effects of varying intensity on EEG morphology as well as dynamics. Output current intensities of 50, 75, 100, 125 and 150 μA were used and remained below AD threshold in all experiments. High frequency stimulation was chosen because of reported anticonvulsive effects with hippocampal and

amygdalohippocampal stimulation in human subjects with refractory temporal lobe epilepsy [19-20].

An ASWA ran in parallel with the EEG data acquisition on a separate PC that computed and plotted dynamical and statistical values in real-time. Once the animal was connected to the ASWA, a training session was used to choose the appropriate electrode combinations to monitor and issue warnings. In this pilot study, upper and lower T-index thresholds were fixed at 5 and 2.662 respectively and a warning was issued when any of the monitored electrode groups showed an entrainment transition.

After a warning was issued, the system was switched from the recording mode to stimulation mode, and a stimulus train was delivered through a hippocampal bipolar electrode. The following parameter setting was chosen for the initial set of trials: output current intensity = 100 μA; frequency = 125 Hz; pulse width = 400 μseconds and duration = 10 seconds. After the stimulus was delivered, the T-index curves were monitored to check the responses of EEG dynmcias.

Results

A. Seizure Predictability

The WROC curves for each animal were estimated from the three warning schemes using 6 different warning horizons. Figure 1 illustrates the WROC curves from the first rat. Closer inspection of these curves shows a consistent superior performance of the ASWA (red line) when compared to the two null seizure warning schemes (blue and green line), with the lower FWR values for almost the entire range of sensitivities.

A summary of seizure warning performance (FWR with sensitivity at least 80%) as a function of SWH is given in Table 2. This performance characterizes the overall (all rats) FWR and seizure warning time (the average of the period from the true warnings issued by the algorithm up to the onset of the subsequent seizures) for ASWA when a sensitivity of 80% or better was required for each rat. With SWH = 1 hour, an FWR of 0.267 per hour (approximately 1 false prediction per 3.8 hours) with the mean seizure warning time 30.7 minutes was observed, while the corresponding FWR for periodic and for random warning scheme are 0.777 and 0.827 per hour, respectively. The FWR decreases when the SWH increases. With SWH = 3 hours, ASWA performed an FWR of 0.116 per hour (approximately 1 false prediction per 8.6 hours) with the mean seizure warning time 69.5 minutes, while the corresponding FWRs for periodic and for random warning schemes are 0.242 and 0.265 per hour, respectively.

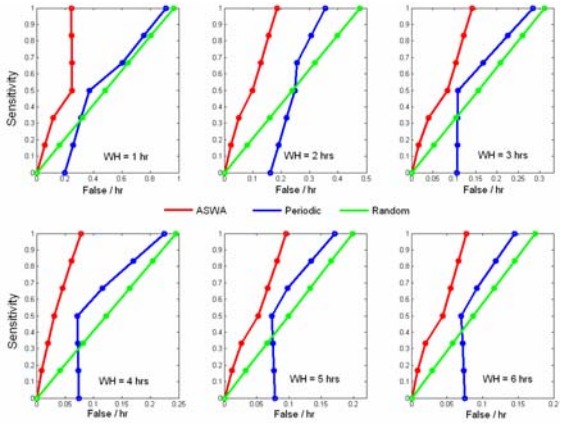

Figure 1: Estimated SWROC curves derived from recordings in the first rat (R-1) for ASWA and two null seizure warning schemes: red line = ASWA; blue line = periodic warning method, and green line = random warning method. The warning horizons applied are from 1 to 6 hours. SWROC curves were smoothed by regression method.

Table 2: Evaluation of overall warning performance of the three test algorithms when sensitivity is set larger than 80% per rat (Sensitivity and Mean Prediction Time columns are from ASWA. Periodic and Random schemes have the similar outcomes for these two characteristics, but with much higher FWRs).

WH (hrs.)	Sensitivity	FWR/hr (ASWA)	Mean Prediction Time (mins.)	FWP/hr (Periodic)	FWR/hr (Random)
1	37/43 = 86.1%	0.267/hr	30.7 (± 18.4)	0.777/hr	0.827/hr
2	37/43 = 86.1%	0.164/hr	54.9 (± 37.7)	0.344/hr	0.402/hr
3	37/43 = 86.1%	0.116/hr	69.5 (± 47.1)	0.242/hr	0.265/hr
4	37/43 = 86.1%	0.080/hr	108.5 (± 60.2)	0.171/hr	0.201/hr
5	37/43 = 86.1%	0.076/hr	133.4 (± 84.6)	0.130/hr	0.161/hr
6	37/43 = 86.1%	0.057/hr	176.9 (± 96.6)	0.107/hr	0.134/hr

For the purpose of estimating predictability power, for each animal, each WROC curve was translated into the performance index AAC. The overall indices are shown in Figure 2. Corresponding to the above observations, the performance indices obtained from ASWA were smaller than those from the two null seizure warning schemes in each of the six SWHs. Statistical tests also revealed that, for each of the WH's, the AAC for the ATSWA was significantly less than that from each of the two naïve warning schemes ($p < 0.01$).

B. EEG Dynamical Responses to Electrical Stimulation

Stimulation exhibited no discernable effects on STLmax values when entrainment was not observed. Stimulation following a dynamical entrainment was found to reset the T-index values and delay the occurrences of impending seizures by a mean of 203.7 (± 89.1) minutes (Figures 3 and 4). In instances where

an entrainment was not reset by stimulation, a seizure occurred within 30 minutes. The mean inter-seizure interval was 2.7±1 hrs during no stimulation and was 7.2±1.3 hrs during post-entrainment stimulation. Stimulations within 10 minutes of the entrainment appeared to be more effective than longer wait periods in their ability to cause dynamical resetting.

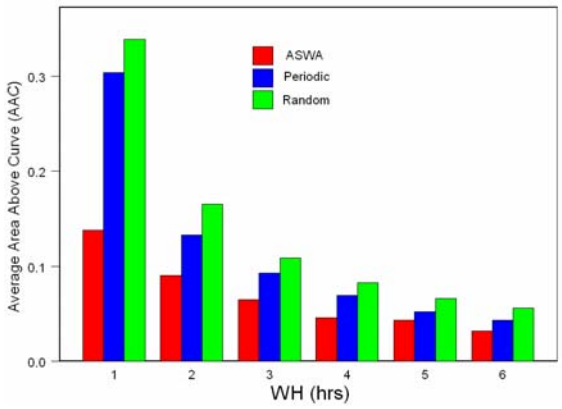

Figure 2: Overall performance index (AAC) from ASWA and two naïve warning schemes with respect to different seizure warning horizons.

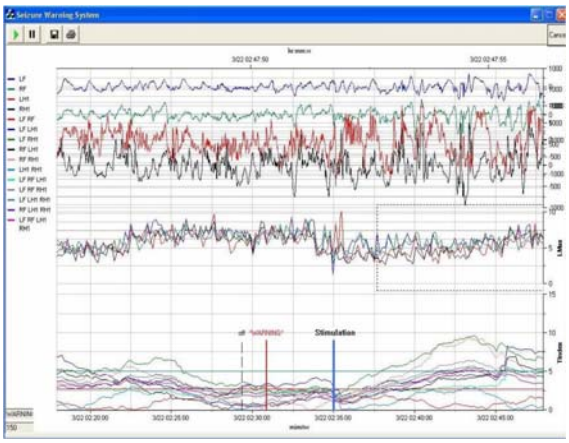

Figure 3: Snapshot of the automated seizure warning system showing examples of stimulation of hippocampus after a warning. Vertical red and blue lines indicate 'seizure warning' and 'stimulation' times respectively. Note the resetting (rise in T-index) after the stimulation.

Discussion

In the present study, we evaluated an EEG-based warning algorithm (ASWA) on 5 CLE rats with long-term (mean duration 456 hours continuous EEG recordings) which included extended seizure-free periods and multiple seizures (see Table 1). The use of the entire continuous EEG recording in each rat eliminated the potential for bias that could occur when an investigator selects epochs for analysis. However, the performance needs to be validated using a larger cohort of animals.

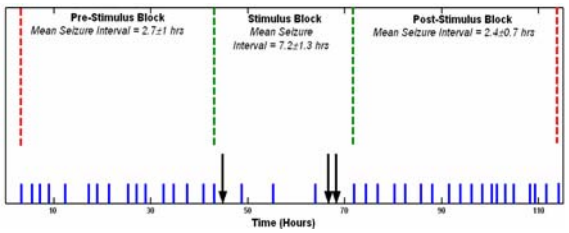

Figure 4: Seizure distributions before and after a stimulus block. Note the change in inter-seizure interval during the stimulus block, compared to the pre-stimulus and post-stimulus blocks.

Similar to Aschenbrenner-Scheibe et al's [18] approach, the evaluation was based on the comparisons with the statistical periodic and random warning schemes, with respect to a characteristic of seizure warning ROC curves (area above curve, AAC). WROC curves describe the performance (with respect to sensitivity and false warning rates) over a range of a parameter, and AAC quantifies the overall warning performance. The results from 5 CLE rats demonstrated that ASWA algorithm significantly ($p<0.05$) outperformed each of the two statistical naïve warning schemes.

The warning performance depends upon the length of the warning horizon (WH). Shortening the WH reduces the sensitivity and increases the false warning rate of an algorithm, while lengthening SWH increases sensitivity and reduces false positive rates. In this study, we evaluated seizure warning performance with WHs of 1 to 6 hours. The analyses revealed that the performance of ATSWA is superior to the naïve warning schemes even when the warnings of impending seizures are more accurate in time (smaller WH). The value of WH will depend upon the clinical application.

Conclusion

These results indicate that it is possible to warn of an impending seizure in the rodent CLE model. They also suggest that the dynamics governing the transition from interictal state to the seizure state are similar to those observed in human temporal lobe epilepsy. In addition, preliminary results from stimulation studies suggest that the mechanism underlying the anticonvulsant effect of hippocampal stimulation may involve dynamical resetting. The ability to warn of impending seizures and intervene to modify the brain dynamics in this model provide an opportunity for developing and testing novel closed-loop intervention techniques directed toward the prevention of impending seizures.

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