Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

Effects of Acute Hippocampal Stimulation on EEG Dynamics

Sandeep P. Nair, J. Chris Sackellares, Deng-Shan Shiau, Wendy M. Norman, Linda K. Dance, Panos M. Pardalos, Jose C. Principe, *Fellow, IEEE*, and Paul R. Carney

Abstract— **Progressive preictal dynamical convergence and postictal divergence of dynamical EEG descriptors among brain regions has been reported in human temporal lobe epilepsy (TLE) and in a rodent model of TLE. There are also reports of anticonvulsant effects of high frequency stimulation of the hippocampus in humans. We postulate that this anticonvulsant effect is due to dynamical resetting by the electrical stimulation. The following study investigated the effects of acute hippocampal electrical stimulation on dynamical transitions in the brain of a spontaneously seizing animal model of TLE to test the hypothesis of divergence in dynamical values by electrical stimulation of the hippocampus.**

I. Introduction

Subacute chronic high frequency electrical stimulation applied at the hippocampus and parahippocampal cortex [1,2] has been shown to have an anticonvulsant effect producing complete blockage of clinical seizures and also cause significant reduction in epileptic activity at the epileptic focus. Similar studies have been conducted using amygdalohippocampal stimulation with comparable results [3]. Other unblinded studies have shown beneficial but smaller effects and long-term effects of hippocampal stimulation without adverse effects [4]. *In vitro* studies have shown that high frequency stimulation has been shown to inhibit neuronal firing by inducing a depolarization block [5,6]. Jerger and Schiff reported a reduction in frequency of occurrence of tonic phase seizure episodes in the CA1 regions of hippocampal slices [7]. Several other mechanisms such as activation of inhibitory pathways and buildup of neurotransmitters have been proposed but the mechanisms underlying the neuromodulatory effects of electrical stimulation are still largely under investigation.

Previous studies have suggested that seizures may not just be abrupt transitions into and out of an abnormal state, but may actually follow a transition that evolves over time periods ranging from minutes to hours [8]. During this preictal transition, dynamical descriptors, e.g. short term Lyapunov exponent (STL_{max}) of multiple cortical regions have been observed to converge. The period following a seizure reveals a sudden divergence in these descriptors suggesting that seizures may be intrinsic mechanisms to revert the brain to a normal (interictal) state. Such a divergence in dynamical measures among brain regions have been shown to be faster and occur more frequently at seizures than at any other periods [9]. These transitions may be detected by spatiotemporal analysis of EEG recorded from multiple regions in the epileptic brain and have been observed in both human patients with epilepsy [8,10,11] as well as spontaneously seizing rodent models of TLE [12]. Iasemidis and Sackellares proposed that external interventions delivered during the preictal period could aid in disrupting the transition to an epileptic seizure thereby alleviating the need for the seizure to happen [9]. The following study investigated the effects of acute hippocampal stimulation (AHS) on dynamical transitions in the brain of a spontaneously seizing TLE animal model, originally described by Lothman and Bertram [13]. We hypothesize that the anticonvulsant effect of hippocampal stimulation may involve reversal of dynamical convergence among brain regions.

Preclinical investigations that will be required to investigate the effects of AHS required identification of an appropriate animal model. For this, we have chosen a spontaneous limbic epilepsy rat model, which has many of the features associated with human TLE including similar electrophysiological correlates, etiology, pathological changes in the limbic system, and seizure induced behavioral manifestations [14,15,16]. The seizures in this model are recurrent, spontaneous, and chronic in nature. In addition, recent work suggests that this model shares many

Manuscript received April 24, 2006. This work was supported by the National Institute of Biomedical Imaging and Bioengineering (NIBIB) through Bioengineering Research Partnership grant (8R01EB002089-03), NIH grant R01-EB004752-01, the University of Florida Children's Miracle Network, the Wilder Epilepsy Research Center and the Department of Veterans Affairs. *Asterisk indicates corresponding author*

*S.P. Nair is with the J. Crayton Pruitt Family Department of Biomedical Engineering, University of Florida, Gainesville, FL 32611-6131 USA (phone: 352-273-5409; fax: 352-273-5411 e-mail: spnair@ufl.edu).

J.C. Sackellares is with the J. Crayton Pruitt Family Department of Biomedical Engineering, University of Florida, Gainesville, FL 32611-6131 USA (e-mail: sackellares@mbi.ufl.edu).

D. Shiau is with the J. Crayton Pruitt Family Department of Biomedical Engineering, University of Florida, Gainesville, FL 32611-6131 USA (e-mail: shiau@mbi.ufl.edu).

W.M. Norman is with the Department of Pediatrics, Division of Neurology, University of Florida, Gainesville, FL 32611-0296 USA (email: normanw@mail.vetmed.ufl.edu).

L.K. Dance is with the J. Crayton Pruitt Family Department of Biomedical Engineering, University of Florida, Gainesville, FL 32611-6131 USA (e-mail: lkdance@mbi.ufl.edu).

P.M. Pardalos is with the Department of Industrial and Systems Engineering, Center for Applied Optimization, University of Florida, Gainesville, FL 32611-6595 USA (e-mail: pardalos@ufl.edu).

J.C. Principe is with the Department of Electrical and Computer Engineering, Computational NeuroEngineering Laboratory, University of Florida, Gainesville, FL 32611-6200 USA (e-mail: principe@cnel.ufl.edu).

P.R. Carney is with the Department of Pediatrics, Division of Neurology, University of Florida, Gainesville, FL 32611-0296 USA (e-mail: carnepr@peds.ufl.edu).

spatiotemporal characteristics of the EEG with human epilepsy [12]. The model is created by inducing prolonged seizures (status epilepticus) through direct stimulation of the ventral hippocampus. After a period of several weeks to a month of recovery, the animals begin to have unprovoked limbic seizures that last for the rest of their lives [14,17].

II. Materials and Methods

A. Subject

Experiments were performed on two month old male Harlan Sprague Dawley rats (n=5) weighing 210-265 g. The first three animals were used to test the effect of hippocampal stimulation on dynamical convergence among brain areas and the last two animals were used to evaluate the effects of stimulation on seizure frequency. Protocols and procedures were approved by the University of Florida Institutional Animal Care and Use Committee. Four 0.8mm stainless steel screws (small parts) were placed in the skull to anchor the acrylic headset. Two of these served as a screw ground electrode and reference electrode. 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 electrodes in the bilateral frontal cortical hemispheres [18]. Electrode pins were collected into a plastic strip connector and the entire headset was glued into place using cranioplast cement (Plastics One, Inc.). Rats were allowed to recover for a week after surgery before further procedures were performed.

B. Model Creation

The rats were then housed in specially made chambers [19] and were subjected to continuous hippocampal stimulation. The stimulus consisted of a series of 10 sec trains (spaced 2 seconds apart) of 1 ms, biphasic square pulses at 50 Hz, at an intensity of 300-400 mA, for 50-70 minutes [13]. 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 hours following an electrical stimulation session. Rats were observed for 12-24 hours 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 limbic seizures developed.

C. Data Acquisition and Stimulation Control

The experimental setup (see Fig. 1) mainly consisted of two parts: (1) the data acquisition and stimulation and (2) Data Analysis and Control. Each animal was connected through a swivel commutator and shielded cable to the recording system, which consists of an analog amplifier (Grass-Model 10), a 12 bit A/D converter (NI, Inc.), and recording software (HARMONIE 5.2, Stellate Inc.), which was synchronized to a time-locked video monitoring unit. 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 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. An online processor estimated values of the dynamical descriptor STL_{max} from the recorded brain regions in real-time and generated control signals based on the convergence of these values to trigger an external stimulator (AM Systems Model 2100).

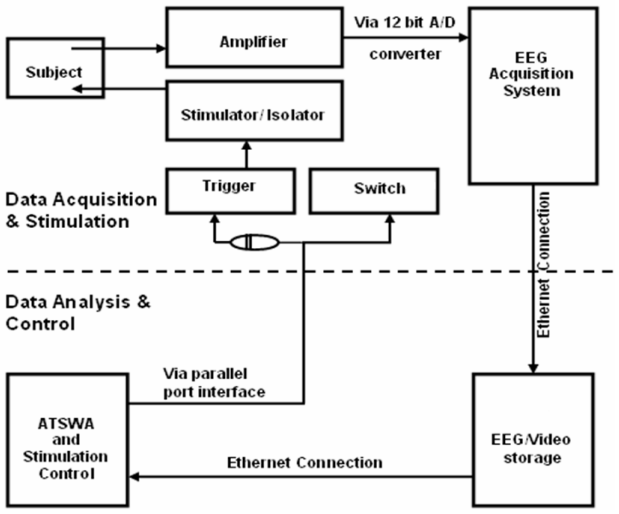

Fig. 1. Schematic of experimental setup

D. Calculation of Dynamical Descriptors

A well-established technique for analyzing the dynamical behavior of a nonlinear dynamical system is to generate a state space portrait of the system where each time-dependent variable of the system is a component of a vector in a properly defined multidimensional (embedded) space [20]. These time-dependent vectors are plotted sequentially in the state space to represent the evolution of the state of the system over time. The Lyapunov exponent is a measure of order in a dynamical system. The largest Lyapunov exponent is defined as the average of local largest Lyapunov exponents L*ij* in the reconstructed state space as follows:

$$L_{\max} = \frac{1}{N} \cdot \sum L_{ij}$$

where N is the total number of the local largest Lyapunov exponents that are estimated from the evolution of adjacent points (vectors) in the state space according to:

$$L_{ij} = \frac{1}{\Delta t} \cdot \log_2 \frac{\left| X(t_i + \Delta t) - X(t_j + \Delta t) \right|}{\left| X(t_i) - X(t_j) \right|}$$

where Δt is the evolution time of the vector in state space [21]. For the estimation of STL_{max} (bits/sec), a state space reconstruction for each EEG channel time series was performed using the method of delays [20] from sequential,

non-overlapping data segments of 10.24 seconds in duration (2048 data points) with embedding dimension of 7 and a time delay of 3. The algorithm for the calculation of STL_{max} for EEG data has been described in detail elsewhere [10]. A new time series called the STL_{max} profiles was created by this procedure with a time resolution of 10.24 sec. The convergence and divergence between pairs of STL_{max} profiles was calculated using the T-test. The T-index for each electrode pair was calculated in each 10 minute epoch by dividing the mean difference of STL_{max} value between the two electrode sites by its standard deviation. For electrode channels *i* and *j*, if their STL_{max} values in a window *Wt* of 60 STL_{max} points are

$$L_i^t = \{STL_{\max i}^{\ t}, STL_{\max i}^{\ t+1}, ..., STL_{\max i}^{\ t+59}\}$$

$$L_j^t = \{STL_{\max j}^{\ t}, STL_{\max j}^{\ t+1}, ..., STL_{\max j}^{\ t+59}\} \quad ,$$

and

$$D_{ij}^t = L_i^t - L_j^t = \{d_{ij}^t, d_{ij}^{t+1}, \mathrm{K}\ d_{ij}^{t+59}\}$$

$$= \{STL_{\max i}^{\ t} - STL_{\max j}^{\ t}, STL_{\max i}^{\ t+1} - STL_{\max j}^{\ t+1}, \mathrm{K}\ , STL_{\max i}^{\ t+59} - STL_{\max j}^{\ t+59}\}$$

the pair-T statistic over the time window W_t between electrode channels *i* and *j* is calculated by:

$$T_{ij}^t = \frac{\left|\overline{D}_{ij}^t\right|}{\hat{\sigma}_d / \sqrt{60}} \quad ,$$

where $\overline{D}_{ij}^t$ and $\hat{\sigma}_d$ are the average value and the sample standard deviation of D_{ij}^t.

E. Stimulation Control

Monitored channel pairs included a hippocampal channel and its contralateral frontal cortical channel (i.e. left hippocampus-right frontal and right hippocampus-left frontal). When the T-index calculated from either pair crossed an upper threshold (U_T = 5, significance level, $\alpha <$ 0.00001) to a lower threshold (U_L = 2.662, significance level, α = 0.01), the ATSWA (see fig. 1), issued a stimulating pulse train via the bipolar electrode in the hippocampal side subjected to continuous stimulation during the model creation phase (see section B). The critical thresholds were chosen from t-distributions based on earlier human studies [11]. The pulse train has the characteristics: output current intensity = 50-150 μA (well below after-discharge threshold of each animal); frequency = 125 Hz; pulse width = 400 μs and train duration = 10 s. The animals showed no perceivable change in behavior during delivery of stimulus. These parameters were partly based on previously reported anticonvulsant effects in human studies [1,2,3].

F. Data Post-processing

Since preliminary analyses revealed that hippocampal stimulation was not always followed by a reversal of observed dynamical convergence among brain regions, we performed a retrospective investigation to look for differences between divergent and non-divergent stimuli. To investigate the differences we estimated a measure of interdependence (average mutual information), also considered as a nonlinear cross correlation function, between electrodes in the monitored pairs. The mutual information (MI) is defined as:

$$I_{XY} = \int_Y \int_X f(x,y) \log_2 \left[\frac{f(x,y)}{f(x)f(y)} \right] dxdy$$

where

f(x,y) is the joint probability density function of X and Y,

f(x) is the probability density function of X, and

f(y) is the probability density function of Y.

The average MI between all monitored pairs was calculated for a 5 minute window immediately prior to the time of stimulus delivery. We used the same window length of 2048 points as that used in the estimation of STL_{max}. We acknowledge accuracy limitations in the histogram method of calculating probability density functions from experimental data [22]. The MI was calculated using standard functions available in the MATLAB® software package.

In two animals, we compared the seizure frequency and incidence during the stimulation phase with their baseline values estimated prior to start of stimulation. Equal periods of time with no stimulation and with stimulation were considered when making the comparison.

III. RESULTS

A total of 36 stimulations (see table 1) were delivered to the first set of rats (N=3) to evaluate the dynamical effects of high frequency stimulation. A reversal of dynamical convergence (rise in T-index) in the monitored electrode pair was observed 77.7% (28/36) of the time. This reversal of convergence was observed to be sustained for a significantly long period of time following the stimulation (see fig. 3), thereby eliminating the possibility of stimulus artifact in the EEG being responsible for the observed phenomenon. Diffused suppression of electrographic activity was also observed following divergent stimulations (see Fig. 2). Eight out of the 36 stimulations had very little effect on the dynamical measures (no divergence), and no discernable changes in electrographic background activity followed these stimulations.

We also evaluated the effect of AHS on seizure frequency in two animals, comparing a baseline seizure frequency before AHS and the seizure frequency during the stimulation phase. We found a significant reduction in seizure frequency (increase in interseizure interval) during the stimulation phase. The mean seizure interval in both animals was increased by around a factor of 3 suggesting a strong anticonvulsant effect of AHS in this animal model. Stimulations in these two animals were also observed to be either divergent or non-divergent in nature. All stimulations

that were followed by the occurrence of a seizure shortly afterwards were observed to be non-divergent in nature.

In all 5 animals included in the study, the average MI among monitored brain regions was significantly different for divergent and non-divergent stimulations. The average MI estimated from a 5 minute EEG epoch immediately before stimulations was found to be significantly higher for divergent stimulations (see fig. 4).

TABLE I
SUMMARY OF EXPERIMENTAL RESULTS

Subject	N_{Stim}	D	ND	II_B (N_{sz})	II_S (N_{sz})
1	12	9	3	-	-
2	12	11	1	-	-
3	12	8	4	-	-
4*	8	5	3	2.7± 1 **(11)**	7.2± 1.3 **(4)**
5*	25	18	7	10.6± 12.4 **(13)**	32.1± 9.7 **(3)**

* Seizure frequency compared in these animals; D-Divergent; ND-Non-divergent; II_B-Baseline interseizure interval in hours; II_S-Stimulation phase nterseizure interval in hours.

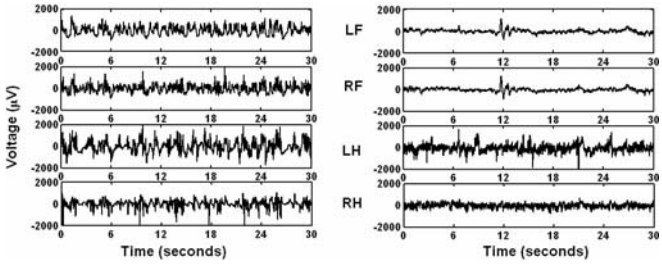

Fig. 2. Representative pre and post stimulation EEG in the recorded electrodes after resetting hippocampal stimulation. LF-left frontal; RF-right frontal; LH-left hippocampus; RH-right hippocampus

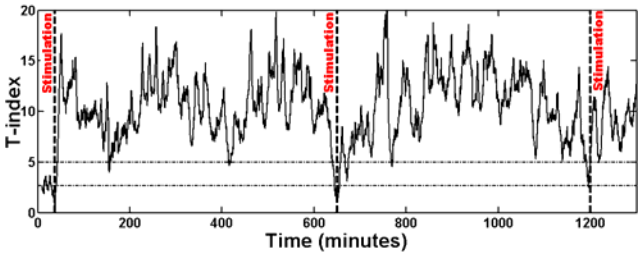

Fig. 3. Reversal of dynamical convergence (T-index) among brain regions by acute hippocampal stimulation

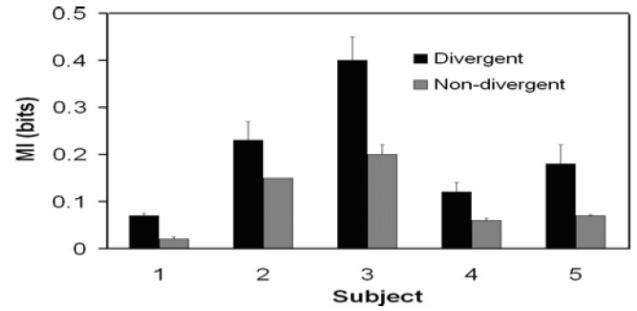

Fig. 4. Comparison of CMI values before resetting and non-resetting stimulations

IV. DISCUSSION

Results of the present study suggest substantial effects of high frequency acute hippocampal stimulation on both EEG dynamics as reflected by the changes in values of T-index calculated from STL_{max}. Preliminary findings also suggest that hippocampal stimulation based on changes in EEG dynamics, seemed to also have an anticonvulsant effect as evidenced by the decrease in seizure frequency and longer seizure free periods in this spontaneously seizing animal model of temporal lobe epilepsy. We suggest that this observed anticonvulsant effect could involve dynamical divergence or reversal of dynamical convergence among brain regions. The difference in MI values calculated before divergent and non-divergent stimulations suggest that more information about the state of the system (brain) could aid in the design of more effective control strategies.

It has been suggested that therapeutic interventions with the goal of dynamically resetting the brain early in the preictal period could alleviate the need for a seizure to occur [9]. The ability of AHS to cause a modulatory effect on EEG dynamics similar to that seen after the occurrence of a seizure and the observation of longer seizure free periods after such changes, leads us to postulate that the anticonvulsant nature of hippocampal stimulation may involve reversal of a preictal dynamical state. Moreover, even though all non-divergent stimulations were not followed by a seizure, it was observed that all stimulations immediately followed by a seizure shortly thereafter failed to reset or reverse the dynamical convergence in the monitored electrode sites. This further leads us to believe that reversal of dynamical convergence among brain areas plays a significant role in the ability of AHS to prevent the occurrence of a seizure. We speculate that the reasons for all non-divergent stimulations not being followed by a seizure could be that the dynamical convergence seen among brain regions that triggered the stimulus may have been false positives.

Suppression of electrographic epileptiform activity in the hippocampus has been shown in both *in vivo* and *in vitro* animal studies as well as human hippocampal slices [6,23,24]. In this study we have observed similar suppression in electrographic activity corresponding to divergent stimulations. It would be interesting to study if the divergence was also accompanied by phase desynchronization as has been reported with *in vitro* hippocampal studies [25].

Failure to cause a reversal in a subset of AHS trials raises questions about avenues for improvement such as more careful design of stimulation parameters, choice of alternate locations, all of which could potentially play significant roles in the outcome of such interventions. The difference in MI values before divergent and non-divergent values suggests that automated stimulation based on more than one descriptor could potentially help achieve the desired state more consistently. Previous studies have proposed and

shown the utility of seizure detection and forecasting based on multiple descriptors [26]. Whether taking into account the MI among brain areas along with other dynamical measures such as T-index of STL_{max} values would provide a better indicator of a seizure susceptible state needs to be investigated. One could also envision a control strategy that continuously monitors the responses to interventions and continues to repeat the process until a desired condition is met or the target state of the brain is reached. More sophisticated control methods such as model based schemes and adaptive intervention schemes that continuously adapt control parameters, targets, according to feedback from the brain could also potentially be useful.

Due to the ad hoc ways that the stimulation has been performed so far, this is considered strong suggestive evidence that more sophisticated methods exploiting the time dimension (i.e. the timing of the stimulation) and stimulation based on measured values of control variables will be successful. More recently studies have used continuous EEG monitoring and pattern recognition algorithms to identify the onset of seizures and apply hippocampal electrical stimulation with the goal of aborting or reducing the seizure activity [27,28]. However it would be more desirable if one could prevent seizure activity from even beginning. We propose that timed acute hippocampal stimulation combined with an online state monitoring system that monitors multiple dynamical descriptors could be a useful therapeutic alternative for controlling seizures in TLE.

ACKNOWLEDGMENT

We would like to thank Angela Hadlock and Dustin Shenk for their technical assistance with animal surgeries and care. Funding has been provided by the Joint NSF/NIH grant 1R01EB004752-01, as well as NIH/NIBIB grant RO1 NS39687-01A1

REFERENCES

[1] Velasco, M. Velasco, A.L. Velasco, D. Menez, L. Rocha, "Electrical stimulation for epilepsy", *Stereotact Funct Neurosurg*., vol. 77, 2001, pp. 223-227

[2] M. Velasco, F. Velasco, A.L. Velasco, B. Boleaga, F. Jimenez, F. Brito, I. Marquez, "Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities", *Epilepsia,* vol. 41, 2001, pp. 58–69

[3] K. Vonck, P. Boon, E. Achten, J. De Reuck, J. Caemaert, "Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy", *Ann Neurol.,* vol. 52 , 2002, pp. 556–65

[4] J.F. Tellez-Zenteno, R.S. McLachlan, A. Parrent, C.S. Kubu, S. Wiebe, "Hippocampal electrical stimulation in mesial temporal lobe epilepsy", *Neurology*, vol. 66, 2006

[5] D.M. Durand, M. Bikson, "Suppression and control of epileptiform activity by electrical stimulation: a review", in *Proceedings of the IEEE,* vol.89(7), 2001, pp. 1065-1082

[6] M. Bikson, J. Lian, P.J. Hahn, W.C. Stacey, C. Sciortino, D.M. Durand, "Suppression of epileptiform activity by high frequency sinusoidal fields in rat hippocampal slices". *J. Physiol*. vol.531, 2001, pp.181-191

[7] K. Jerger, S.J. Schiff, "Periodic pacing of an in vitro epileptic focus". *J. Neurophysiol.,* vol.73, 1995, pp. 876-79

[8] L.D. Iasemidis, J.C. Sackellares, "Chaos theory and Epilepsy". *The Neuroscientist* vol. 2, 1996, pp.118-126

[9] L.D. Iasemidis, D.S. Shiau, J.C. Sackellares, P.M. Pardalos, A. Prasad, "Dynamical Resetting of the Human Brain at Epileptic Seizures: Application of Nonlinear Dynamics and Global Optimization Techniques", *IEEE Trans. Biomed. Eng*. vol.51(3), 2004, pp. 493-506

[10] L.D. Iasemidis, J.C. Sackellares, H.P. Zaveri, W.J. Williams, "Phase space topography of the electrocorticogram and the Lyapunov exponent in partial seizures". *Brain Topogr*. vol. 2, 1990, pp. 187-201

[11] L.D. Iasemidis, D.S. Shiau, W. Chaowolitwongse, J.C. Sackellares, P.M. Pardalos, J.C. Principe, P.R. Carney, A. Prasad, B. Veeramani, K. Tsakalis, "Adaptive epileptic seizure prediction system". *IEEE Trans. Biomed. Eng*. vol.50(5), 2003, pp. 616-627

[12] S.P. Nair, D.S. Shiau, W.M. Norman, D. Shenk, W. Suharitdamrong, L.D. Iasemidis, P.M. Pardalos, J.C. Sackellares, P.R. Carney, "Dynamical Changes in the Rat Chronic Limbic Epilepsy Model". *Epilepsia* vol. 45 (S7), 2004, pp. 211-212

[13] E.W. Lothman, E.H. Bertram, J. Kapur, J.L. Stringer, "Recurrent spontaneous hippocampal seizures in the rat as a chronic sequela to limbic status epilepticus", *Epilepsy Res*., vol.6, 1990, pp. 110-118

[14] E.H. Bertram, J. Cornett, "The ontogeny of seizures in a rat model of limbic epilepsy: evidence for a kindling process in the development of chronic spontaneous seizures". *Brain Res*. vol. 625, 1993, pp. 295-300

[15] M. Quigg, E.H. Bertram, T. Jackson, E. Laws, "Volumetric magnetic resonance imaging evidence of bilateral hippocampal atrophy in mesial temporal lobe epilepsy". *Epilepsia* vol. 38, 1997, pp. 588-594

[16] M. Quigg, M. Staume, M. Menaker, E.H. Bertram, "Temporal distribution of partial seizures: Comparison of an animal model with human partial epilepsy". *Ann. Neurol*. vol. 43, 1998, pp. 748-755

[17] E.H. Bertram, J.F. Cornett, "The evolution of a rat model of chronic spontaneous limbic seizures". *Brain Res*. vol. 661, 1994, pp. 157-162

[18] G. Paxinos, C. Watson, "The Rat Brain in Stereotaxic Coordinates" fourth ed., Academic Press, 1998

[19] E.H. Bertram, J.M. Williamson, J.F. Cornett, S. Spradlin, Z.F. Chen, "Design and construction of a long-term continuous video-EEG monitoring unit for simultaneous recording of multiple small animals, *Brain Res Protoc*., vol.2(1) (1997) 85-97

[20] F. Takens, Detecting strange attractors in turbulence, in *Dynamical systems and turbulence: lecture notes in mathematics*, : D.A. Rand, L.S. Young, Eds., Springer-Verlag, 1981, pp. 366-381

[21] A. Wolf, J.B. Swift, H.L. Swinney, J.A. Vastano, "Determining Lyapunov exponents from a time series", Physica D. vol. 16, 1985, pp. 285-317

[22] A.M. Fraser, H.L. Swinney, "Independent coordinates for strange attractors from mutual information", Phys Rev A vol. 33, 1986, pp. 1134–1140

[23] J. Lian, M. Bikson, C. Sciortino, W.C. Stacey, D.M. Durand, "Local suppression of epileptiform activity by electrical stimulation in rat hippocampus *in vitro*", *J . Physiol.,* vol. 547(2), 2003, pp. 427-434

[24] T. Loddenkemper, H. Luders, "Mechanisms and efficacy of deep brain stimulation in epilepsy". *in: Presurgical assessment of the epilepsies with clinical neurophysiology and functional imaging*, Rosenow F, Luders H, eds., 1st ed. Elsevier, 2004, pp. 539–570

[25] D.M. Durand, E.N. Warman, "Desynchronization of epileptiform activity by extracellular current pulses in rat hippocampal slices", *J. Physiol.*, vol. 480(3), pp. 527-537

[26] M. D'Alessandro, R. Esteller, G. Vachtsevanos, A. Hinson, J. Echauz, B. Litt, "Epileptic seizure prediction using hybrid feature selection over multiple intracranial EEG electrode contacts: a report of four patients", *IEEE Trans. Biomed. Eng*. vol.50(5), 2003, pp. 603-615

[27] E.H. Kossoff, E.K. Ritzl, J.M. Politsky, A.M. Murro, J.R. Smith, R.B. Duckrow, D.D. Spencer, G.K. Bergey, "Effect of an External Responsive Neurostimulator on Seizures and Electrographic Discharges during Subdural Electrode Monitoring", *Epilepsia*, vol. 45(12), 2004, pp. 1560-1567

[28] I. Osorio, M.G. Frei, S. Sunderam, J. Giftakis, N.C. Bhavaraju, S.F. Schaffner, S.B. Wilkinson, "Automated seizure abatement in humans using electrical stimulation", *Ann. Neurol.*, vol.57, 2005, pp. 258-268