REAL-TIME CONTROL OF EPILEPTIC SEIZURES

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Abstract: In this paper, we utilize a measure of brain dynamics, namely the short-term largest Lyapunov exponent (STL_{max}) calculated in real-time, to test the hypothesis of dynamic resetting of the epileptic brain with deep brain stimulation (DBS) and antiepileptic drugs (AEDs) treatments in epileptic animals as a method for closed-loop control of epileptic seizures. This measure is estimated from analysis of electroencephalographic (EEG) recordings at multiple brain locations in chronically epileptic rats (DBS studies) and acute status epilepticus (SE) rats (AED studies). Techniques from optimization theory and statistics are applied to select optimal sets of brain sites, whose dynamics are then measured over time to study their entrainment/disentrainment. Results from DBS in the thalamic centromedial nucleus suggest that 130 Hz electrical stimulation can result in disentrainment of the optimal set of electrodes mimicking dynamical resetting of the epileptic brain by seizures. Results from AED studies indicate that the observed abnormal spatio-temporal dynamical entrainment in SE is reversed by AED administration (resetting of brain dynamics). These results support the hypothesis of dynamical resetting of the epileptic brain following successful treatments with DBS in chronically epileptic rats and AEDs in SE-induced rats.

Introduction

Epilepsy is the second most common neurological disorder after stroke, and affects at least 50 million people world-wide. Approximately 60% of new onset epilepsy cases respond to existing antiepileptic drugs (AEDs) but 40% are pharmaco-resistant, with seizures that cannot be fully controlled with available medical therapy or without unacceptable side effects [1]. Thus, there are at least 25 million people world-wide for whom the development of more effective epilepsy treatment paradigms would be greatly beneficial.

In the last decade, substantial progress has been made towards the study of the human brain by utilizing concepts and measures from nonlinear dynamics. Within this framework, a significant amount of effort has been made towards understanding the mechanisms underlying the spontaneous initiation and termination of epileptic seizures. The central concept is that seizures represent transitions of the epileptic brain from its "normal" (less ordered -chaotic) state to an abnormal (more ordered) state and back to a "normal" state, along the lines of spatio-temporal chaos-to-order-to-chaos transitions. The hallmark of this research is the ability to predict epileptic seizures, in the order of tens of minutes prior to their clinical or electrographic onset [2]. A unified dynamical view about epileptic seizures has begun to emerge where seizures are manifestations of a recruitment of brain sites in an abnormal hyper-synchronization. The onset of such recruitment occurs long before a seizure and progressively culminates into a seizure. Therefore, seizures appear to be bifurcations of a neural network that involves a progressive coupling of the focus with the normal brain sites during a preictal period (before a seizure) that may last days to tens of minutes. This research has provided useful insights into the progressive preictal entrainment, and the subsequent post-ictal (after a seizure) disentrainment of the epileptic brain's spatio-temporal EEG activity, under the idea of "dynamical resetting of epileptic brain" [3], [4]. In status epilepticus, seizures may continue to occur as the dynamical entrainment persists and the seizure resetting mechanism is not effective enough to disrupt it.

Status epilepticus (SE) is usually defined as greater than 30 minutes of continuous seizure activity or two or more sequential seizures without full recovery of consciousness between seizures. An estimated 250,000 cases of SE occur in the USA annually, and the prognosis for patients whose seizures cannot be rapidly controlled is poor [5]. Treatment of SE has traditionally involved intravenous administration of drugs used to treat chronic epilepsy. Status epilepticus still carries a 10-12% morbidity rate and a further risk of significant morbidity if not arrested promptly [6]. Only about 55% of patients in SE are successfully controlled by their first treatment regimen [7]. New drugs for the treatment of SE are sorely needed and are primarily tested using *in vivo* animal models of SE.

Treiman *et al*. [8] has described a sequence of five progressive EEG changes in generalized convulsive status epilepticus (GCSE) in humans as well as in experimental models in rats, which are predictive of the response to treatment with an AED [9], [10]. The EEG changes of SE appear in the following order: I) discrete electrographic seizures, II) waxing and waning or merging seizure activity, III) continuous ictal discharges, IV) continuous ictal discharges punctuated

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by relatively flat periods, and V) periodic epileptiform discharges on a relatively flat background. Recovery is possible at any SE stage.

As the ability to predict leads to the possibility of control, we were motivated by our previous hypothesis of brain resetting at seizure points to evaluate the effectiveness in brain resetting of deep brain stimulation and antiepileptic drugs. We postulated that successful treatment of epilepsy with deep brain stimulation (DBS) or antiepileptic drugs (AEDs) might have exactly the same result, that is to reset the brain. We herein present the first results that appear to support this hypothesis. The analysis is carried out in real-time on chronically epileptic rats for the DBS studies and in three animal models of acute status epilepticus for the AED studies.

Materials and Methods

The brain is a highly complex spatio-temporal nonlinear system. The EEG, being the output of such a system, has statistical properties that depend on both time and space. The state space analysis of the EEG in epilepsy reveals the presence of an attractor with nonlinear characteristics during seizures (ictal states) [2]. Lyapunov exponents, measures of chaos and rates of generation/destruction of information, quantify the average exponential convergence or divergence of the trajectories of such an attractor in the state space. Due to the non-stationarity of EEG data, only dynamical analysis of short segments of the EEG is meaningful. The short-term largest Lyapunov exponent (STL_{max}) can thus be defined to approximate the largest Lyapunov exponent over time. Following [12], [13], STL_{max} is the average of local Lyapunov L_{ij} in the state space:

$$STL_{\max} = \frac{1}{N_\alpha} \bullet \sum_{\alpha} L_{ij} \qquad (1)$$

where N_α is the total number of the local Lyapunov exponents estimated from the evolution of adjacent points $X(t_i)$ and $X(t_j)$ (vectors) in the state space, reconstructed by the method of delays from each EEG segment according to:

$$L_{ij} = \frac{1}{\Delta t} \bullet \log_2 \frac{|X(t_i + \Delta t) - X(t_j + \Delta t)|}{|X(t_i) - X(t_j)|} \qquad (2)$$

where Δt is the evolution time allowed for the vector difference $|X(t_i)-X(t_j)|$ to evolve to the new difference $|X(t_i+\Delta t)-X(t_j+\Delta t)|$. If Δt is given in sec, then STL_{max} is in bits/sec. The STL_{max} values are calculated over 10.24 second segments of EEG data per recording area of the brain over time [12-14].

The spatial dynamics of the epileptic transition are captured by consideration of the relations of the STL_{max} between different cortical sites through the use of a student's *t*-test; conditions for such a test were satisfied [4]. The STL_{max} of the involved sites in this transition are converging to similar values long prior to the transition. We have called such participating sites "critical sites", and the convergence observed over time at these sites "spatial dynamical entrainment". Subsequently, a T-index value is calculated over a window of 60 consecutive STL_{max} values over time within each pair of electrode sites. The entrainment observed in an electrode pair is considered to be statistically significant (at a confidence level $\alpha = 0.01$) when the T-index value falls below the corresponding critical threshold value ($T_c = 2.33$, with 59 degrees of freedom). The critical brain sites of the transition are determined by the use of optimization [2], [4]. Finally, the average T-index over all pairs of the critical sites is estimated over time and is used as a global measure of the level of dynamical entrainment.

A software program (ESWP) was custom developed with EegSoft Inc. that is able to calculate STL_{max} values, select critical sites of electrodes, and estimate T-index values in real-time. Also included within this application was the development of software that controls the timing and outputs of an A-M Systems Model 2300 Digital Stimulus Isolator that can use the T-index of critical electrode sites as a control signal for electrical stimulation, see the flow chart in Figure 1.

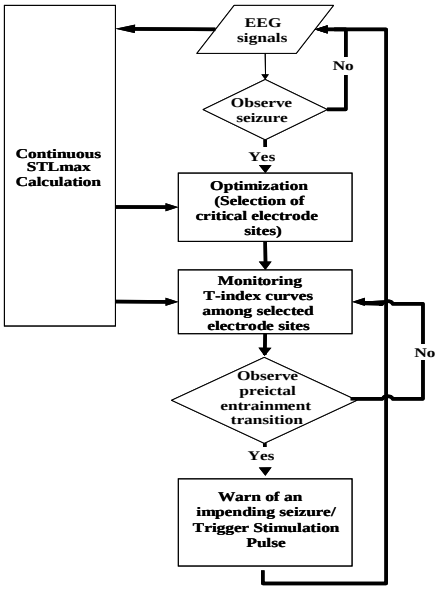

Figure 1: Flow Chart of ESWP program

Adult male Sprague-Dawley rats (300-350 g) obtained from Harlan Labs were used in the study. Rats were housed singly after surgery, with food and water available ad lib and a 24 hour diurnal light cycle maintained, with lights on from 07:00 to 19:00 each day. Rats were anaesthetized by an intraperitoneal (IP) injection of 87 mg/ kg ketamine plus 13 mg/kg xylazine and implanted with either a depth electrode wire array (DBS studies) or epidural screw electrodes (AED studies).

Following surgical implantation, rats were allowed to recover at least 48 hours prior to experimentation. For all experiments, rats were placed in a Plexiglas recording chamber and connected to a Grass-Telefactor Beehive® Millennium EEG machine by a flexible cable suspended from the top of the cage, with an interposed

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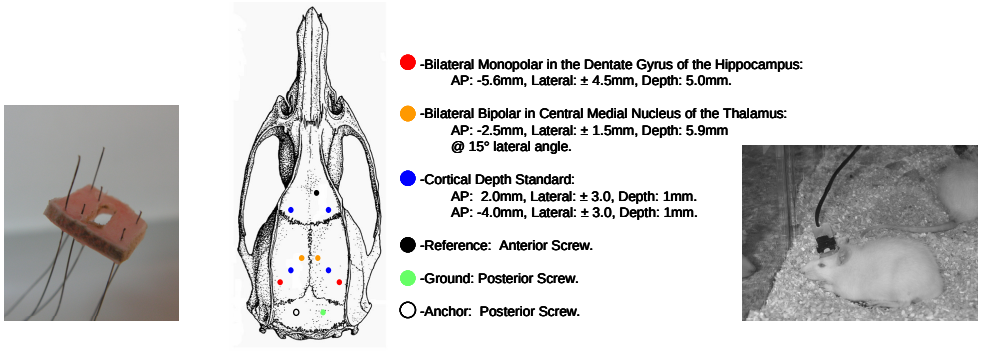

Figure 2: Depth electrode array, stereotaxic coordinates of implantation for DBS studies, and implanted rat.

commutator to allow rats free access to food and water without twisting the cable. A baseline EEG of at least one hour was recorded prior to any experimentation, thereafter video/EEG recordings were performed continuously and data were analyzed in real-time with the use of the ESWP program and all STL_{max} and T-index data saved for further off-line analysis. The EEG recordings were performed with a referential montage and were digitized at 200 Hz and stored in ASCII format for further off-line analysis

DBS Studies

For the DBS studies, a custom built depth electrode array consisting of six Teflon coated Tungsten wires (175 µm diameter) was implanted stereotaxically along with two bipolar twist stimulation electrodes as shown in Figure 2. Electrode position was determined from the rat atlas of Paxinos and Wilson [15].

Chronic epilepsy was developed over a period of weeks after an episode of SE was induced utilizing the lithium/pilocarpine model. In short, rats were injected subcutaneously with lithium chloride (3 mmol/kg) approximately 20 hours prior to pilocarpine (30 mg/kg) and allowed to progress into SE. Acepromazine (15 mg/kg) was given IP to each rat after 30 minutes of continuous seizure activity in order to aid with survival. Surviving rats were then video/EEG monitored weekly until chronic epilepsy was established. Once, chronic epilepsy was established each rat was video/EEG monitored with EEG data analyzed in real-time with the ESWP program. A one minute train of high frequency stimulation (130 Hz square bipolar cathodic first 750 µA constant current, 100 µsec pulse width) was delivered to the left thalamic stimulating electrode. At least four stimulation trains were delivered to each rat over a period of 24 hours with at least six hours between stimulation trains. A non-epileptic (normal implanted non-SE) rat was also stimulated to serve as a control. All STL_{max}, T-index, and a logfile of stimulation data were saved for further off-line analysis.

AED Studies

For the AED studies, six epidural screw electrodes made from #0-80 x 1/8 inch stainless steel screws were placed at the stereotaxic locations that correspond to the cortical depth standard, reference and ground locations as shown in Figure 2.

Rats were induced into status epilepticus by one of three different methods: cobalt/homocysteine (CoHCT), lithium/pilocarpine (LP), or kainic acid (KA). In each model, rats were established into SE and treated at various stages determined by EEG morphology with an AED cocktail that consisted of diazepam (10mg/kg) and phenobarbital (25 mg/kg).

For the CoHCT model, the method described by Walton and Treiman [11] was used, where during surgical implantation, ~2.5 mg of powdered cobalt was placed onto the dura under the left anterior screw electrode (F3) to create a seizure focus. The seizure focus typically was evident by the detection of focal epileptiform spikes or bursts on the EEG at the electrode site where the cobalt was placed between 5 and 9 days after surgical implantation. Once epileptiform activity was present, an IP injection of homocysteine thiolactone (5.5 mmol/kg) was done to induce SE.

For the LP model, rats were injected IP with lithium chloride (3 mmol/kg) 20 hours prior to the subcutaneous injection of pilocarpine (30 mg/kg) to induce SE. For the KA model, rats were injected IP with kainic acid (15 mg/kg) to induce SE.

Results

DBS Studies

We stimulated three epileptic and one control rat with multiple 130 Hz DBS trains. We herein present results from the real-time analysis of the referential depth EEG recordings from one epileptic and the control rat. In each of the cases dynamic resetting was apparent in many of the selected electrode pairs. In Figure 3, the STL_{max} (panel A) and T-index (panel B) profiles from the corresponding dynamical analysis of the EEG are shown for the epileptic rat for the electrode pair left hippocampus vs. left thalamus. The STL_{max} of the EEG from these electrodes are statistically entrained (below the horizontal dotted line $\alpha = 0.01$) prior to the stimulation train shown at time = 0. There is artifact created by the one minute stimulation that affects the T-index values up to the 11 minute mark because of the 60

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point window for the calculation of the T-index and this is noted in the plot. The disentrainment (dynamical resetting) is evident after the stimulus artifact zone and persists up to 20 minutes after the stimulation has ended.

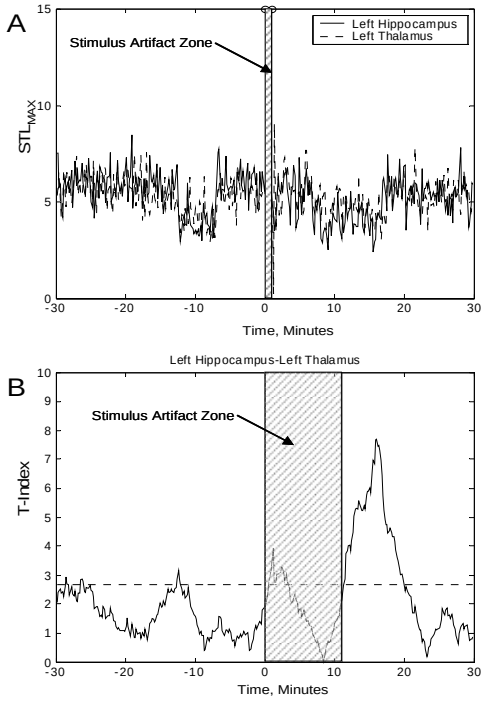

Figure 3: DBS in an epileptic rat. **A:** STL_{max} profile of the left hippocampus (solid) and the left thalamus (dotted) **B:** T-index profile of A. 130 Hz stimulation at time = 0.

Corresponding results are shown in Figure 4 for the control rat with STL_{max} and T-index profiles also shown for the left hippocampus vs. left thalamus electrode pair. The stimulation train is delivered at time = 0 and the stimulus artifact zone is noted. Dynamical resetting is clearly evident following the artifact zone and is achieved for nearly 40 minutes after the stimulation has ended.

AED Studies

A total of 14 rats were used in the AED treatment studies: 4 rats in the CoHCT model, 4 rats in the LP model, and 6 rats in the KA model (see Table 1 for SE Stage treatment breakdown vs. success).

Table 1: Success of AED treatments vs. SE model and EEG Stage

	Stage I	**Stage III**	**Stage V**
CoHCT	1/2	0/1	1/1
LP	2/2	0/1	1/1
KA	2/2	2/4	0/0

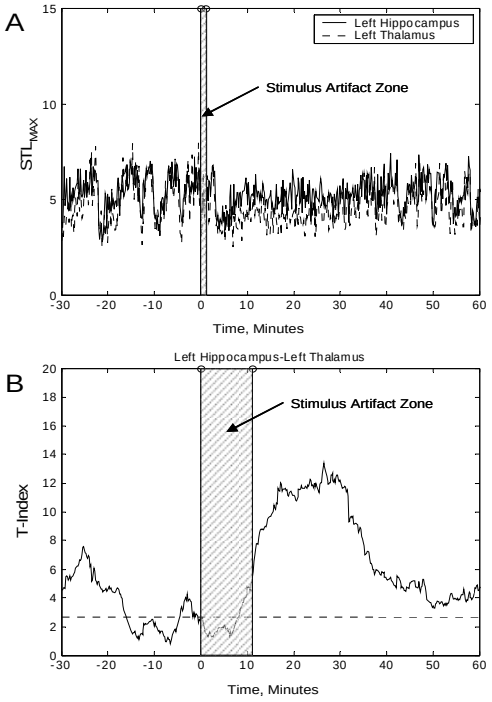

Figure 4: DBS in a control rat. **A:** STL_{max} profile of the left hippocampus (solid) and the left thalamus (dotted) **B:** T-index profile of A. 130 Hz stimulation at time = 0.

We herein present results from the real-time analysis of the referential epidural EEG recordings from one successfully treated rat from each model and one unsuccessfully treated rat from the CoHCT model. In all models, successful treatment (verified by visual inspection of EEG morphology) resulted in dynamical resetting of electrodes sites.

In Figure 5, the T-index profiles were generated from the STL_{max} values for the non-focal electrode pairs P3 vs. P4 (panel A) and the focal electrode pair F3 vs. non-focal P4 (panel B) for a CoHCT rat successfully treated in SE Stage V. It is noteworthy that the two non-focal sites are entrained during all first four SE stages. The two normal brain sites disentrain within minutes after Stage IV and remain disentrained thereafter. They further disentrain after the administration of the AEDs. Dynamical disentrainment holds for more than 6 hours in this non-focal electrode pair, whereas in panel B, disentrainment of the focal/non-focal electrode pair holds for about 1 hour after the AED, and then oscillates around the statistical significance level for the remainder of the recording.

In Figure 6, the T-index profiles were also generated from STL_{max} values for the non-focal electrode pair P3 vs. P4 (panel A) and the focal electrode pair F3 vs. P4 (panel B) for a CoHCT rat unsuccessfully treated in SE Stage I. Note that dynamical entrainment is shown for both cases, however, following AED administration only the non-focal electrode pair resets (panel A) while the focal electrode pair remains entrained (panel B).

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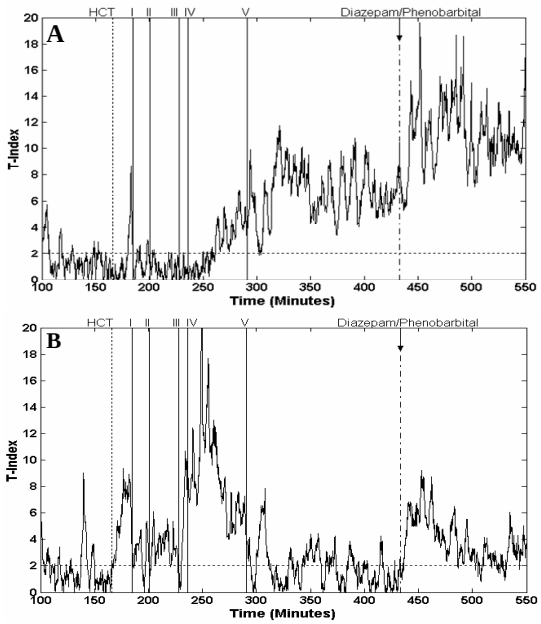

Figure 5: Successful AED treatment in an SE Stage V CoHCT rat. **A:** T-index of non-focal pair F3 vs. F4 **B:** T-index of focal F3 vs. non-focal P4 pair.

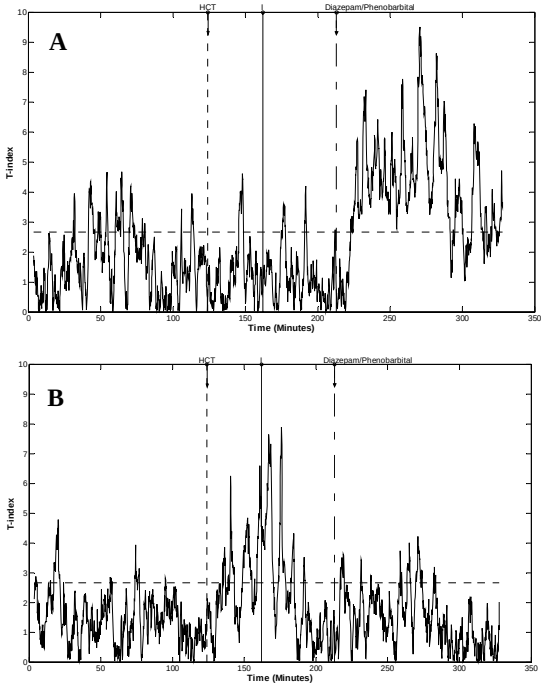

Figure 6: Unsuccessful AED treatment in an SE Stage I CoHCT rat. **A:** T-index of nonfocal pair F3 vs. F4 **B:** T-index of focal F3 vs. non-focal P4 pair.

In Figure 7, the global T-index profiles generated from all four electrodes in an LP (panel A) and KA (panel B) rat successfully treated in SE Stage V and III respectively. Note that there is a persistent global dynamical entrainment prior to the treatment in both cases and a global dynamical resetting following the AED treatment.

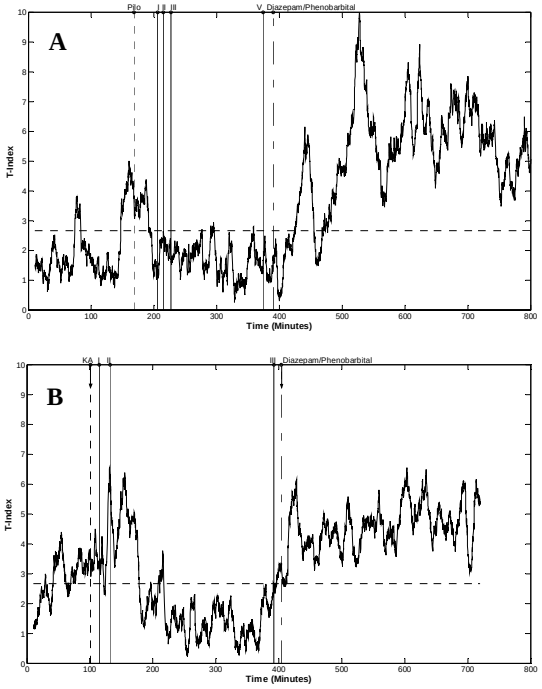

Figure 7: Successful AED treatments in **A:** global T-index of SE Stage V LP rat **B:** global T-index of SE Stage III KA rat.

Discussion

DBS Studies

Dynamical resetting was observed in both chronically epileptic rats and a normal control rat when exposed to a one minute train of deep brain stimulation at 130 Hz in the left centromedial nucleus of the thalamus. The amount of resetting was greater in the control rat and persisted for a longer amount of time than the epileptic rats (~40 minutes vs. ~20 minutes) before returning to baseline levels. This could be indicative of a time constant within the pathologic epileptic state of the brain which could be an important factor for consideration of control schemes that utilize dynamic entrainment as a trigger for delivering DBS for closed-loop control of epileptic seizures. This finding supports the hypothesis that the abnormal hypersynchronization among sites within the epileptic brain can be reset to a more normal chaotic state with deep brain stimulation and supports the hypothesis that deep brain stimulation can mimic the dynamical resetting seen by a seizure.

AED Studies

From evaluation of antiepileptic drug treatments in three rat models of status epilepticus it appears that a successful treatment by administration of the AEDs diazepam and phenobarbital results in dynamical disentrainment. It is important to note that within the CoHCT model (a model of secondarily generalized SE) upon AED administration, a dynamical disentrainment in focal/non-focal electrode sites is less pronounced than the disentrainment in non-focal electrode sites.

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This implies that the abnormal functional bond of the focus with normal sites is stronger and more difficult to break than the one between normal sites. This observation was also validated by the unsuccessful treatment and lack of dynamical resetting seen in the rat that did not respond to AED treatment in the CoHCT model. In the LP and KA models (primarily generalized SE models) a global dynamical resetting was correlated with a successful treatment. The resetting effect was present at all EEG Stages of SE, independent of the SE model tested.

Conclusions

High frequency deep brain stimulation has drawn much attention as a potential controlling mechanism for epileptic seizures in closed-loop systems. We have shown for the first time evidence that DBS can effectively reset brain dynamics from the abnormally hypersynchronous epileptic state of the brain to a more normal chaotic state. We have also shown a very good correspondence between the measures defined from mathematical analysis and clinical morphology of EEG with the treatment efficacy of an AED in stopping status epilepticus. It appears that focal/non-focal dynamical disentrainment of electrode sites is indicative of treatment efficacy in secondarily generalized SE while global disentrainment is necessary in primarily generalized SE. These results indicate that the measures used herein, as well as other measures within the framework of nonlinear dynamics and chaos theory, may provide useful information for the development of new treatment modalities utilizing DBS paradigms for refractory epilepsy, as well as for the evaluation and development of new antiepileptic drugs for treatment of status epilepticus that maximize efficacy in dynamical resetting of the brain.

Acknowledgments

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