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Pre-Ictal Entropy Analysis of Microwire Data from an Animal Model of Limbic Epilepsy

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***Abstract*: Epilepsy is a common neurological disorder that can have damaging effects in the brain including over 50% loss of neuronal activity in the hippocampal regions of the CA1 and CA3. The pre-ictal period was studied in an animal model of limbic epilepsy using Shannon entropy and correlation analysis. The primary aim was to uncover underlying relative changes in signals between the Dentate Gyrus and CA1 areas of the bilateral hippocampus. Preliminary entropy analysis results included dynamical changes between channels in the Dentate Gyrus and channels in the CA1 region at and around the time of the seizure.**

Keywords—**limbic epilepsy, latent period, Shannon entropy**

I. INTRODUCTION

Epilepsy affects 3-5% of the population worldwide. Epilepsy is a neurological disorder characterized by recurrent and unprovoked seizures. An individual loses awareness when experiencing a complex partial seizure due to the spread of the seizure through both temporal lobes and subsequently impairing memory. [1] Of all cases, approximately 60% respond favorably to anti-epileptic drugs. [2] Regardless of age, sex or race, the harmful effects of limbic Epilepsy can be caused by past infections, vascular malformations, hamartomas and gliomas. Head trauma in the form of hemorrhaging or contusion in the brain often leads to the development of limbic Epilepsy after a number of months to years. This span of time is known as a latent period when cellular and network changes are thought to occur precipitating the onset of seizures. In epileptogenesis over 50% of the neurons in the hippocampal regions of the CA1 and CA3 are lost. Neuronal loss also occurs with the granule cells in the Dentate Gyrus; accompanying these changes is a loss of inhibitory neurons, excitatory neurons and excitatory axonal sprouting. [1]

The Chronic Limbic Epilepsy rat model imitates human limbic epilepsy with the initial insult to the brain quiescent period and resultant seizures later in life. The manner in which these seizures develop is thought to be a result of structural changes in the brain such as the strengthening of excitatory networks, loss of inhibitory neurons or suppression of GABA receptors. [3] Since little is known about the time period over which the changes occur, it is proposed that detectable changes occur gradually within the brain over the latent period eventually causing the later hypersynchronous seizure activity.

The link between the nature of the pre-ictal period and the electrical changes manifested in the brain are not well characterized. The abnormal mode of communication, a characteristic of seizures, is demonstrated by large-amplitude wave discharges occurring over a large hemisphere of the brain.

The preictal period in an animal model of limbic epilepsy is studied using Shannon entropy measurements. The goal of this research is to characterize underlying changes in signals between the Dentate Gyrus and CA1 areas of the bilateral hippocampus.

II. METHODOLOGY

A. Experimental epilepsy animal model:

The model used is the chronic limbic epilepsy rat model [4] which involves applying an initial stimulatinginsult to the brain, and leads to recurrent seizures 4-8 weeks later. Animal studied were approved by the University of Florida IACUC.

Thirty-two tungsten microwire electrodes were implanted in the CA1/CA2 and Dentate Gyrus areas of the hippocampus bilaterally, with ~8 microwires implanted into each area. The electrodes were implanted in two rows spaced 420 μm apart and each electrode in the row was spaced 210 μm apart. Data was digitized at 16 bits and recorded continuously at 12207 Hz using custom written acquisition software and a Tucker-Davis Pentusa DSP that employed a hardware bandpass filter set from 0.5 Hz to 6 kHz.

Approximately one to two weeks of baseline data was recorded after the animal had sufficient time to recover from surgery. The animal was then stimulated in the manner prescribed for the Chronic Limbic Epilepsy animal model. [4, 5] Recording began again within a day of stimulation and continued until after the animal spontaneously seized. In the case of the control animal, the animal was not stimulated, simply recorded for roughly the same time period. All animals were continuously video monitored to screen for seizures.

After sufficient data was gathered the animal was euthanized and the brain was then examined for pathological changes and electrode placement through MRI and histology. MR imaging was implemented with a 17.6 Tesla MRI machine to illustrate bilateral anatomical changes, which occurred over the latent period.[6]

B. Analysis Methods

With continuous and high resolution data dynamical changes of each channel to observe how signals change specifically around the seizure (short-term) as well as the long term changes over the latent period. We used the measures of linear correlation and Shannon Entropy.

Shannon Entropy was used to measure the degree of order in the time series of the data. Analysis was primarily focused on the order of each channel indicating the relative organization of the different parts of the bilateral hippocampus relative to each other. Equation (1) was used to calculate entropy [2, 7]:

$$H_n = - \sum p_i^{(n)} \log p_i^{(n)} \qquad (1)$$

The variable p represents the probability distribution of entropy in the time series. Entropy was calculated with a window resolution of 6000 points ; in total, two hours of data was analyzed. The time series includes data of the actual seizure phase, identified through video monitoring and lasting approximately one minute. Also included was the phase that and builds up to the seizure and post-seizure data. Average entropy values for each channel were calculated for specific sets of two-minute time series in order to examine how the average entropy gradually changes preceding the ictal period.

III. RESULTS

In the time series, analysis indicates that dynamical changes occurred in the hippocampus with regard to relative values of entropy. In Fig. 1, the time series of the entropy values were plotted for specific channels during a relatively normal period of functioning for the rat. The data displays higher values of entropy in the Left Dentate Gyrus. It was also apparent that channels within the left and right CA1 exhibit lower values of entropy and more order. In contrast, the entropy calculation in all channels was observed to greatly decrease upon the onset of the seizure. The spike indicating the 'pop,' or onset of seizure, was dramatic as evidenced by the large spike in Fig. 2. After the spike, the entropy of all channels slightly increased during the quiescent period, but subsequently demonstrated some dynamic activity in post-seizure (Fig. 3).

In Fig. 2, channels in the Left Dentate Gyrus appeared steady until the spike at the beginning of the seizure. Similarly, channels left and right CA1 respectively were steady until the spike at 5732 seconds. After the spike, these regions suddenly increased in entropy for approximately 10 seconds and then decreased again. Fig. 3 illustrates data for the two minutes following the seizure. Around t = 5800 s channels located in the right CA1, suddenly became less ordered. Also, before the increase in entropy at t = 5800 s, channels in the Right Dentate Gyrus was less ordered than the left Dentate Gyrus immediately following the seizure. Such a result is intriguing since in the time series of a normally functioning brain, the left Dentate Gyrus was generally characterized as less ordered than the right Dentate Gyrus. After t = 5800 s however, a dynamic change occurred: the left Dentate Gyrus suddenly became less ordered than the right Dentate Gyrus, resuming the general behavior during the interictal period (Fig. 2). In addition, all the channels around t = 5822 s decreased in entropy particularly in the left CA1. After this brief spike, the channels returned to their previous entropy state.

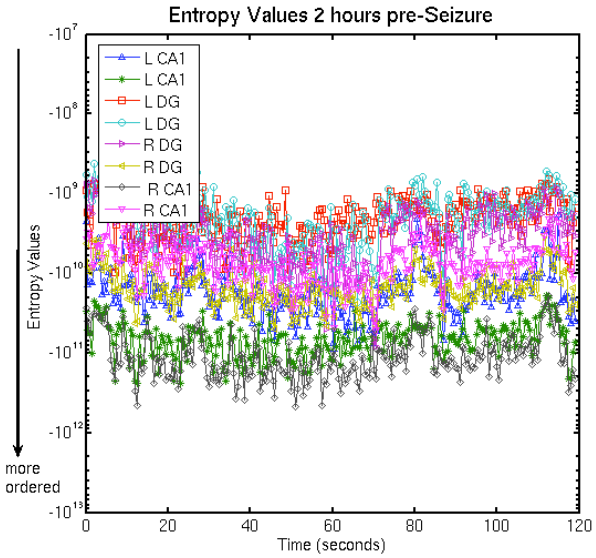

Figure 1. Entropy Values approximately 2 hours prior to Seizure Onset. Two channels from each region are shown in the graph. The entropy values are higher (less ordered) in the DG relative to CA1 in the interictal period.

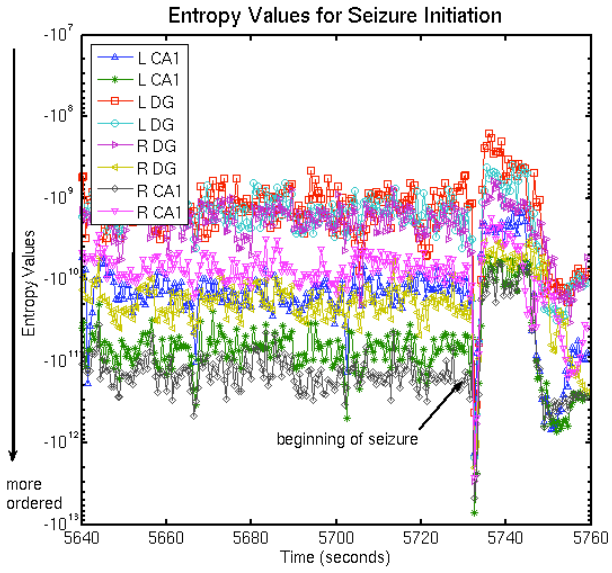

Figure 2 Entropy Values around Seizure Initiation. Two selected channels from each region are shown in the graph. The overall entropy of all the channels suddenly decreases sharply at the onset of the seizure, indicating a sudden change of orderedness followed by an increase in entropy during the quiescent period immediately prior to seizure onset.

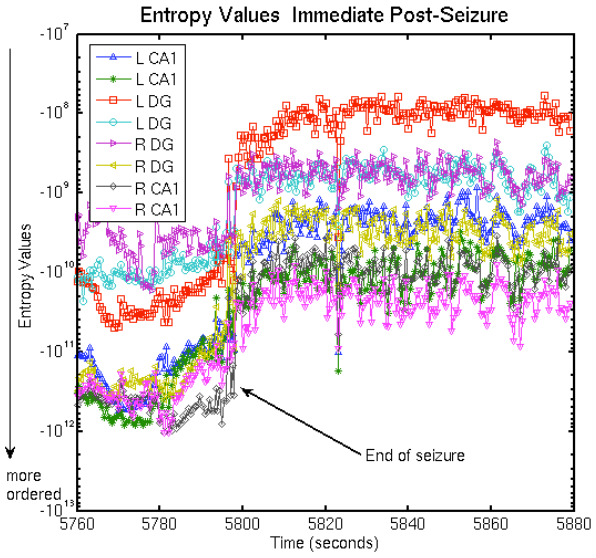

Figure 3 Entropy Values immediately after a Seizure. Two selected channels from each region are shown in the graph. Immediately following the seizure, the right DG is less ordered than the left. The left DG resumes the less ordered state relative to the right. An interesting spike occurs around approx. 5820 seconds as all channels temporarily decrease in entropy.

IV. DISCUSSION

The focus in this work is the study of the dynamical changes in entropy and correlation within the hippocampus over the latent period to characterize subtle changes during epileptogenesis.

According to EEG data from Steuer, et al [2] the time series became more ordered during a seizure; however, the relative orderedness of the hippocampus before, during, and after a seizure, is a different result. Further in-depth analysis will explore the gradual change in average entropy of each channel in leading to the seizure.

IV. ACKNOWLEDGEMENT

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