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Coherence Analysis Over the Latent Period of Epileptogenesis Reveal that High-Frequency Communication is Increased Across Hemispheres in an Animal Model of Limbic Epilepsy

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Abstract—**A total of 32 microwire electrodes were implanted bilaterally into the hippocampus of Sprague-Dawley rats, which were then stimulated in the manner prescribed for the Chronic Limbic Epilepsy Model. After the initial seizure brought on by the stimulation, the animals were recorded at a high sampling rate (~12 kHz) for the entire duration of the latent period. Coherence was calculated across channels in both stimulated (and later seizing) animals and non-stimulated (and thus non-seizing control) animals. Average coherence over time was greatest in intrahemispherical electrode pairs in both stimulated and non-stimulated animals. However, the 200-800 Hz band displays increased coherence interhemispherically and the 0-200 Hz band displays decreased coherence interhemispherically: this occurs only in stimulated animals.**

Keywords—**limbic epilepsy, latent period, coherence analysis**

I. INTRODUCTION

Epilepsy affects 3-5% of the population worldwide, affecting persons indiscriminately of age, sex, or race. In the vast majority of cases, seizures arise from medial temporal structures that have been damaged (due to injury or illness) months to years before onset of seizures.[1] Over this "latent period," cellular and network changes are thought to occur which precipitate the onset of seizures. Loss of inhibitory neurons, excitatory axonal sprouting, or loss of excitatory neurons 'driving' inhibitory neurons are all thought to contribute to epileptogenesis. [1]. It is not understood exactly how these seizures come about, but is thought to be due to structural changes in the brain, as in the loss of inhibitory neurons, the strengthening of excitatory networks, or the suppression of GABA receptors. [2] The time period over which these changes occur and seizures develop, the so-called 'latent period' has not been widely characterized. Using an animal model of temporal lobe epilepsy, we studied the latent period using Magnitude Squared Coherence to uncover underlying relative changes in signal frequency content bilaterally between the Dentate Gyrus and CA1 areas of the hippocampus.

Our findings indicate that the coherence of frequency bands common within the hippocampus and between hippocampal regions changes during the latent period; specifically, coherence in the 200-800 Hz band between hippocampampi increases, while the coherence in the 0-200 Hz band between hippocampi decreases.

II. METHODOLOGY

A: Experimental Epilepsy Animal Model

All animal experiments were approved by the University of Florida IACUC. The Chronic Limbic Epilepsy [3, 4] model is a rodent model of limbic epilepsy in which the animal is kindled into status epilepticus for 1 hour. Following a recovery period of 12-24 hrs, spontaneous seizures occur within 2-8 weeks, which are recurrent and chronic.

A total of 32 tungsten microwire electrodes were implanted in the CA1 and Dentate Gyrus subfields of the hippocampus bilaterally, with ~8 microwires implanted into each field. The electrodes are implanted in two rows which are spaces 420 μm apart, and each electrode in the row space 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, which employed a hardware bandpass filter set from 0.5 Hz to 6 kHz.

Two weeks of baseline data were recorded after the animal had sufficient time to recover from electrode implantation. The animal was then kindled in the manner prescribed for the Chronic Limbic Epilepsy Animal model.[3] Continuous recording began within a day of kindling, and continued until after the spontaneous electrographic and behavioral seizures. A control animal was recorded using the same protocol. All animals were continuously video monitored to screen for seizures.

After sufficient data was gathered, the animal was sacrificed and the brain perfused for MR Imaging on a 17.6 Tesla MRI machine; these images are shown in this paper to point out bilateral anatomical and hippocampal neuronal ensemble changes which occurred over the latent period of epileptogenesis reported by our group [5]

B: Coherence

Coherence analysis [6], which quantifies the portion of signals in the frequency spectra which have the same power in the same frequency bin, can be used as a general tool to determine frequency power changes occurring in a system. A robust increase or decrease in Coherence can indicate whether two time series have quantifiably similar frequency properties over a given time period.

Microwire data taken from an animal model is prone to non-stationarities and artifact, which must be taken into account when doing the analysis. We thus restrict our FFT window size to 4096 points (1/3 second), and averaging three segments (with 50% overlap) to enhance SNR and still

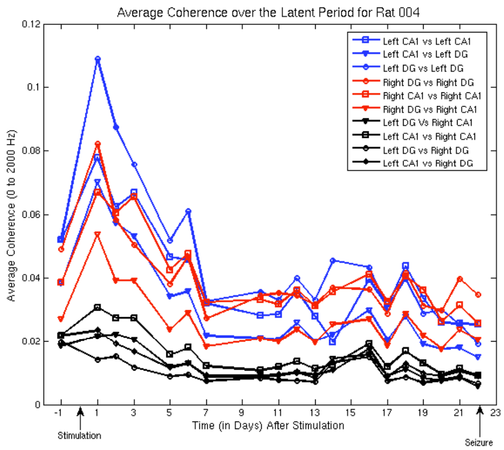

Figure 1: Averaged Coherence for a Stimulated animal, covering prestimulation, and post-stimulation to the time of development of seizures. This figure shows Coherence from 0–2000 Hz averaged over data taken from microelectrodes which were solely within left and right hemispheres (blue and red lines, respectively) , and calculated from channels taken from both left and right hemispheres (black line). We see that the intra-hemispherical coherence (red and blue lines) is higher than the inter-hemispherical coherence (black line), and immediately post stimulation we see greatly increased intrahemispherical coherence in both left and right hemispheres, but not interhemispherically. After a period of ~ 5-7 days, this increased coherence has decreased to pre-stimulation values and remains relatively steady to the time of development of seizures.

remain within reasonable stationary bounds. Thirty-minute segments of data taken from the same time of day (early afternoon) were analyzed. Coherence was determined for each electrode pair for every day prior to onset of seizures; coherence was calculated for baseline pre-stimulation data, and then continuously immediately after stimulation. Coherence results between each channel pair were then grouped according to which regions were being compared. A total of ten region-to-region comparisons were made, with some comparisons being entirely within a single hemisphere, with others across hemispheres.

III. RESULTS

A: Inter- vs Intra-Hippocampus Average Coherence

Average coherence (from 0-2000 Hz) was higher within hemispheres than across hemispheres. For the entire time period analyzed, for stimulated and non-stimulated animals, with the activity in the left and right hemispheres being ~2-6 times more coherent than the inter-hemispherical activity. This is reassuring since the electrodes within the Dentate Gyrus and CA1 of each hemisphere are in closer proximity to each other, and *connectively should* be more coherent than on the other hemisphere. Figure 1 illustrates for averaged coherent activity for a typical stimulated animal showing an increase in coherence within the left and right hemispheres respectively immediately after stimulation. This lasts approximately 5-7 days after which the coherence levels decrease to pre-stimulation levels and remain relatively

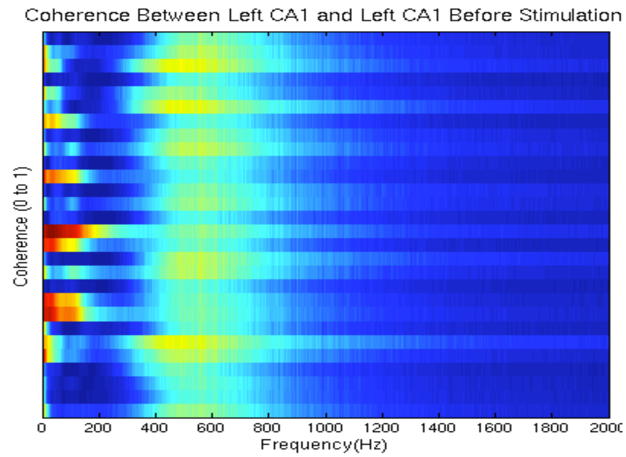

Figure 2: Coherence of all Left CA1 channels vs Left CA1 channels taken before stimulation. The channel to channel pairing is the y-axis, the x-axis is frequency (in Hz), and the color is the Coherence of the channel-channel pairing at that particular frequency. One sees that there are two main bands of coherence in these channel pairs: one from 0-200 Hz, and one from 200 – 800 Hz; these bands exist in all region-to-region comparisons.

steady until the onset of seizures 14-16 days later. Average coherence, however is not a satisfactory measure in terms of uncovering dynamical changes and differences between stimulated and non-stimulated animals in terms of how communication in and between hemispheres has changed.

B. Coherence in High/Low Frequency Bands

We thus turn to an examination of particular bands of coherence: looking at coherence from one area to another and plotting each channel's coherence as a function of frequency, there are two main peaks in most data, one between 0-200 Hz and one within 200-800 Hz, as shown in Figure 2.

If one then follows the evolution of these two bands of coherence across time, different patterns emerge allowing

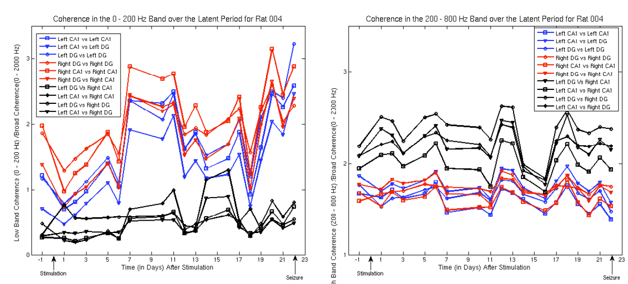

Figure 3: Low- and High-Band Coherence for a stimulated animal. The Low-Band Coherence (left) figure shows the change over time of the coherence over 0-200 Hz normalized by the average coherence in the 0-2000 Hz band as was displayed in Figure 1 for a stimulated animal. The High-Band Coherence (right) figure shows the change over time of the coherence in the 200-800 Hz band also normalized by the average coherence in the 0-2000 Hz band. The inter-hemispherical coherence is decreased for 0-200 Hz activity but increased for 200-800 Hz activity.

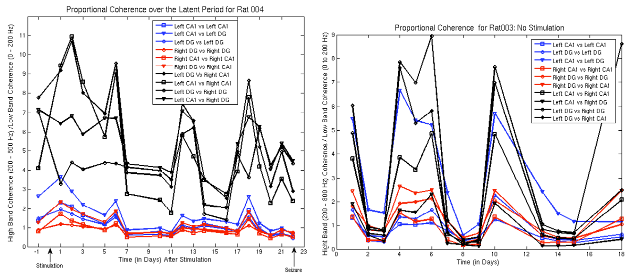

Figure 4: Proportional Coherence for a stimulated animal (left) and a non-stimulated animal (right), obtained by dividing the Average Coherence from 200-800 Hz by the Average Coherence at 0-200 Hz. For the stimulated animal (left), across hemispheres there is unequal weighting of the coherence of high and low frequency bands: the coherence in the high band is significantly greater (2-11 times) than the low band. This difference does not occur in the non-stimulated animal (right).

one to differentiate stimulated vs non-stimulated and inter-hemispherical vs. intrahemispherical data. For *stimulated* animals one sees a difference in the relative coherence in the 0-200 Hz band compared to the 200-800 Hz band between inter-hemispherical and intra-hemispherical Coherence pairs, as shown in Figure 3. While the intra-hemispherical coherence increases for the 0 – 200 Hz band, the inter-hemispherical coherence increases for the 200-800 Hz band.

By dividing the coherence in the 200-800 Hz band by the coherence in the 0-200 Hz band, an idea of the proportional strength of the coherence increase in the 200-800 Hz band in stimulated animals over the latent period is obtained. See Figure 4 for proportional coherence in stimulated and nonstimulated animals.

IV. DISCUSSION

We present here coherence analysis results over the latent period of epileptogenesis, showing that different frequency bands change differently for stimulated vs. control animals. Average Coherence is decreased across hemispheres in both stimulated and non-stimulated animals, but the proportion of coherence across hemispheres in the 200-800 Hz band is significantly increased (2 to 11 times) over that of the 0-200 Hz band in stimulated animals. In non-kindled animals, there is no distinction between intra and inter-hemispherical banding. As the non-stimulated animal has a similar range, this suggests that Coherence in the 200-800 Hz band is being suppressed within each hemisphere. This has implications in network remodeling: is the local network dynamics changing to suppress high-frequency coherence, and is that affecting the long-range connectivity across the entire brain? While the results are preliminary (n = 3) and more work must be done to confirm the findings, the finding is significant.

V. ACKNOWLEDGMENT

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