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A Method for Actively Tracking Excitability of Brain Networks using a Fully Implantable Monitoring System

Dean R. Freestone, Sam N. Long, Stephen Frey, Paul H. Stypulkowski, Jonathon E. Giftakis, and Mark J. Cook

Abstract— **This paper introduces a new method for estimating the excitability of brain networks. The motivation for this research was to develop a system that can track pathological changes in excitability, in diseases such as epilepsy. The ability to track excitability may provide a method for anticipating seizures and intervening therapeutically. Four normally healthy canines were implanted with the Medtronic Activia PC+S deep brain stimulation and sensing system. The devices were used to probe the circuit of Papez, with electrical stimulation in the anterior nucleus of the thalamus to measure evoked potentials in the hippocampus. The canines were given three different dosage levels of anti-convulsant medication in an attempt to manipulate the excitability of the network. The results showed changes in the morphology of the evoked potentials, following a circadian profile and reflecting times of drug delivery.**

I. Introduction

This paper introduces a new method for estimating excitability of brain networks. The motivation for estimating the excitability of the brain is embedded in the notion that hyper-excitability is a necessary condition for the occurrence of epileptic seizures [1]. If this is true, then the ability to track excitability could lead to a method for anticipating seizures. Furthermore, if one can reliably estimate brain excitability, it may be possible to use this information to titrate therapies and on-demand interventions, such as drug treatments or modulatory electrical deep brain stimulation (DBS).

Epilepsy is a disease of the brain characterized by spontaneous recurrent seizures. Approximately 1-2% of the world's population have epilepsy and approximately 30% of epilepsy sufferers do not received adequate control with conventional therapies [2], [3]. For these people, potentially life threatening seizures may occur without warning, thereby severely restricting their quality of life. There exists an enormous potential to improve on standard treatments with a seizure warning system, ideally, a method of intervention based on an early warning signal to prevent these episodes.

Preseizure hyper-excitability has been observed using a number of different imaging modalities including function magnetic resonance imaging, near infrared spectroscopy, positron emission tomography, brain impedance, intracranial electroencephalography (iEEG) and others [4], [5], [6], [7], [8]. A critical element for enabling use excitability measurements in a clinical tool is making an ambulatory monitoring system, ideally fully implantable. The iEEG has the potential to be incorporated into an implantable device, which is why it is the chosen measurement modality in the field of epileptic seizure prediction. However, a major difficulty has been in decoding the complicated iEEG signal and extracting the key components of excitability. We have addressed this challenge by actively probing the brain, to excite features that reveal the responsiveness, or excitability, of networks. The notion of probing the brain is in line with other work in the literature [9], [10], [11], [12], [13].

The Medtronic Activa PC+S (or Brain Radio) DBS system has the ability to stimulate and record responses, and provides a solution to the problem of long-term monitoring. Details of the system are outlined in [14], [15]. This system offers a solution to a chronic fully implantable system that is capable of probing brain networks and using this information to monitor the titration of modulatory therapy [16], [17].

This paper describes the first phase of a pre-clinical trial that uses the Activa PC+S system as a monitor for cortical excitability in canines. This first phase is a control study using normally healthy greyhounds. Novel aspects of the paper are in regard to the duration of monitoring, the use of anti-convulsant medication in an attempt to manipulate the excitability, and the use of the Activa PC+S device for tracking excitability.

II. Methods

This section describes the protocol, detailing the surgery, the stimulation and recording methods, drug modulation, and data analysis procedure.

A. Surgery

Four normal greyhounds were enrolled in the study. Imaging using 1.5T MRI was performed on the day prior to surgery with fiducial arrays attached to the frontal bone for trajectory planning. The targets chosen were the anterior

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D. R. Freestone is with the NeuroEngineering Laboratory, Department of Electrical and Electronic Engineering, and The Center for Neural Engineering, The University of Melbourne, Parkville, VIC, Australia, 3010

S. N. Long is with the Faculty of Veterinary Science, The University of Melbourne, 250 Princes Hwy, Werribee, VIC, Australia, 3030

S. Frey is with Rogue Research Inc., 4398 St-Laurent blvd, Suite 206, Montreal, Quebec, Canada, H2W 1Z5

P. H. Stypulkowski, J. E. Giftakis are with Medtronic Neuromodulation, Minneapolis, Minn., USA

M. J. Cook is with The University of Melbourne, Department of Neurology, St. Vincent's Hospital Melbourne, Fitzroy, VIC, Australia, 3065, . See `http://www.neuroeng.unimelb.edu.au/` for email.

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(rostral) nucleus of the thalamus (ANT) (Medtronic NuMed, 4 contact primate electrode) and the hippocampus (Medtronic 3387, 4 contact DBS electrode) on the ipsilateral side in each dog. The surgical targets are nodes in the circuit of Papez, which has been shown to be involved in mesial temporal lobe epilepsy. The Brainsight system from Rogue Research Inc. was used to plan the trajectory and conduct the stereotactic surgery. Postoperative CT scanning and coregistration with the preoperative MRI was then performed to confirm placement of the electrodes before the dogs were recovered.

All dogs recovered normally ($>$ 4 weeks period) and showed no neurological deficits post implantation. In Subject 3 postoperative CT showed movement of electrodes. This subject was not further considered in this study.

B. Stimulation and Sensing Protocol

A bipolar pair of electrodes in the ANT lead was chosen for stimulation and a differential pair of electrodes in the hippocampus was chosen for recording. The electrode configuration for stimulation and recording was based on the proximity to the targets in accordance with the postoperative CT images. The electrical stimulation consisted of biphasic pulses, delivered at a rate of 2 Hz. The stimulation rate was sufficiently low to allow the transient activity from each of the stimuli to decay away before the arrival of any subsequent stimuli. The stimulator was set in constant Voltage mode, with an amplitude of 3 V and a pulse width of 300 μs.

The evoked-potentials (EPs) were recorded with a sampling rate of 422 Hz in 33 s windows, starting every 15 mins over the duration of the testing period. This allowed 66 electrical-evoked potentials to be recorded over the 33 s window. The duration of the window and interval between windows was chosen to allow for a sufficient number of trials (66) for averaging with a reasonable time resolution (15 mins) to track excitability changes, whilst allowing for a full day of data to be stored on the device.

C. Anti-Epileptic Drug Modulation

After 4 days of base-line testing, each dog received 3 levels of the anti-epileptic drug, Levetiracetam (Keppra), over the time course of the experimental protocol. The dosages were 20 mg/kg, 30 mg/kg and 40 mg/kg, which were given to the canines 3 times per day at 12 am, 8 am, and 4 pm. This agent was chosen due to the suitable half life in canines, allowing maintenance of drug level steady states. Although this is a well accepted treatment of epilepsy, the mechanism of action is largely unknown. Nevertheless, we hypothesized that the drug would decrease neural excitability.

D. Data Analysis

The data analysis consisted of 2 simple steps. The first was computing the averaged EP for each of the 33 s windows, and the second was extracting scalar features of the averaged EPs that are descriptive of their shape.

The averaged EPs were computed by aligning each individual EP using the stimulation artifacts. The artifacts were extracted from the signals by first up sampling the data by a factor of 4, then computing the forward difference of the recorded time series before applying a threshold of 4 standard deviations from the mean. The time of the first sample to

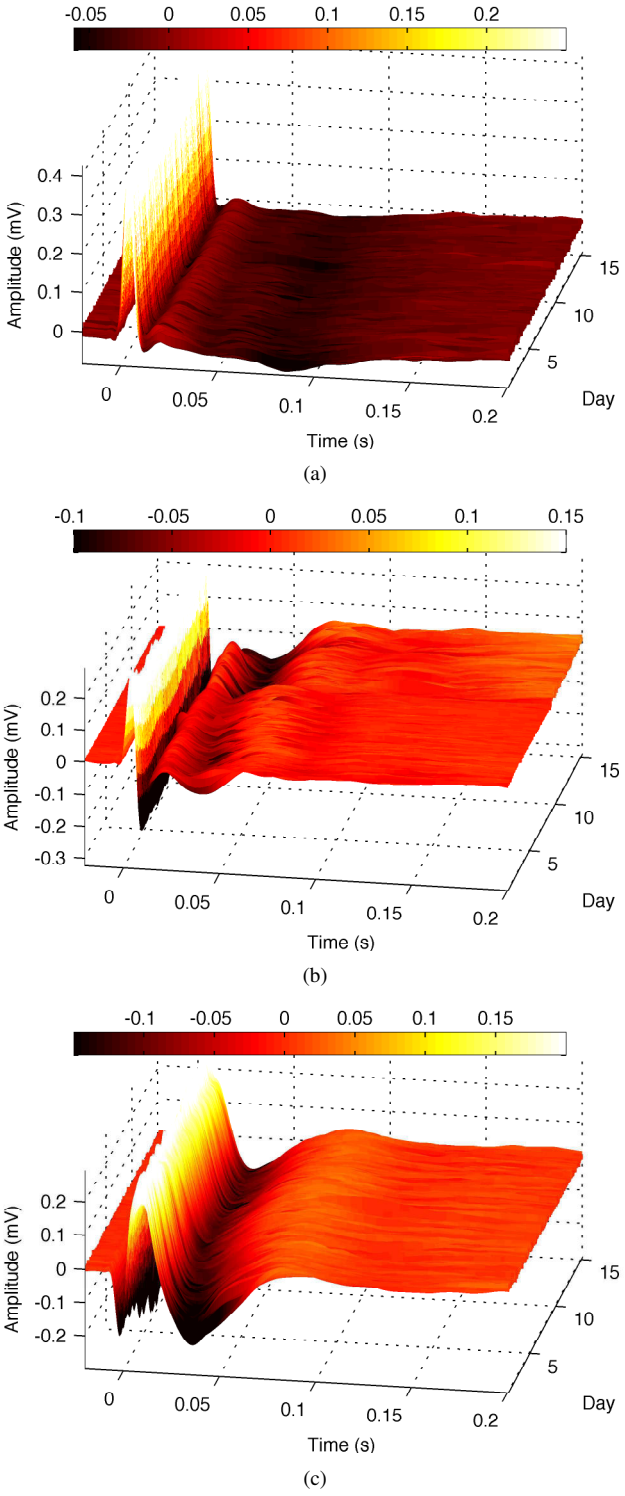

Fig. 1. Averaged EPs Over Time. The surface is constructed by concatenating all averaged EPs. The x-axis indicates the time course of each averaged EP. The y-axis shows the variation of averaged EPs of the experimental protocol with a time resolution 15 minutes. The z-axis indicates the amplitude of the averaged EPs. (a), (b), and (c) indicate the EPs are from Subjects 1, 2, and 4, respectively.

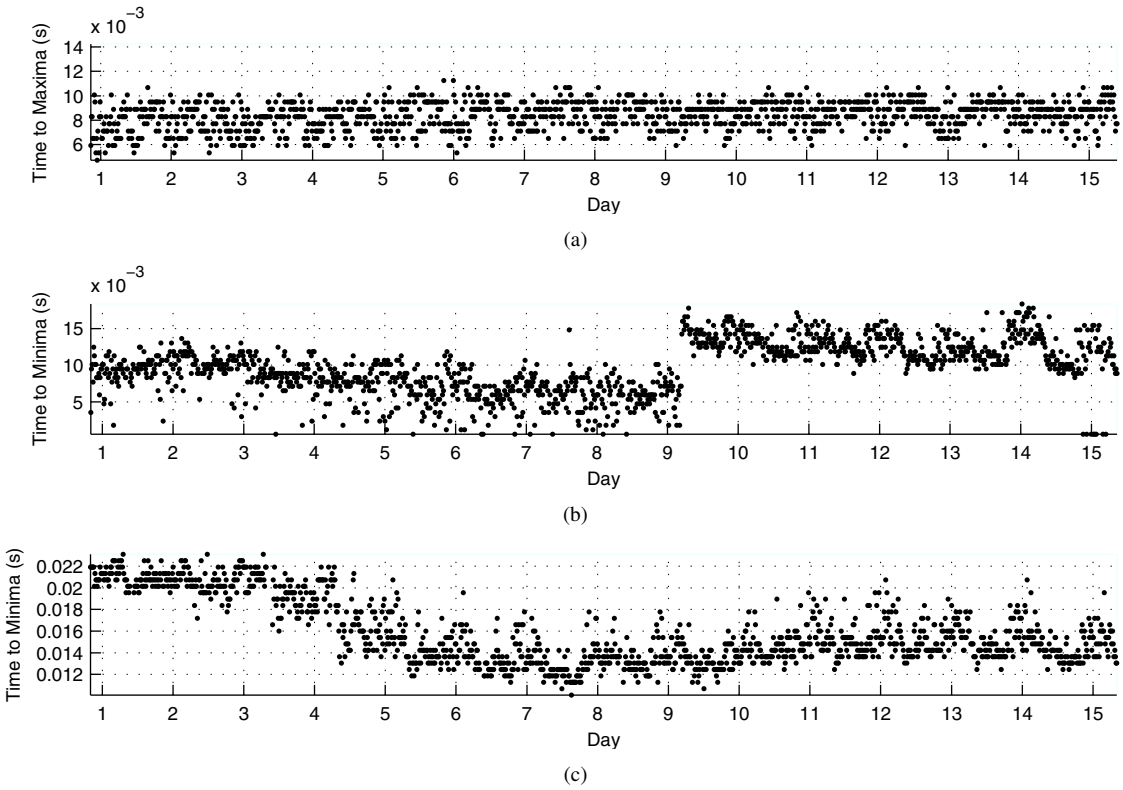

Fig. 2. Time to Reach Peaks of the Averaged EPs. Each subfigure shows the time to reach the dominant peak in the averaged EP. The time resolution of the of each data point is 15 mins. (a), (b), and (c) indicate the results are from Subjects 1, 2, and 4, respectively.

cross this threshold for each stimuli was used to segment the stimuli. The EPs were extracted with windows of 20 ms before and 200 ms after each stimulation artifact detection.

The features of the averaged EPs that were considered were the amplitude of the largest peak, and the time to reach the peak relative to the stimuli. These were chosen since they are likely to vary with changes in excitability within the network, and for computational simplicity. Only the latency of the dominant peak relative to the stimulus is presented in the results section due to space restrictions.

III. Results

In this section we present the results from the experiments. Figure 1 shows the morphology of the averaged EPs over the experimental period. The figure illustrates some variation in the morphology between subjects. This is likely due to a variation in the anatomical location of the stimulation and recording electrodes. Figure 1(b) shows two abrupt changes in the shape of the EP in subject 2. The reason for the changes are currently unknown, but may be due to a shift in the location of the electrodes from vigorous movements.

Figure 2 shows the times to reach a dominant peak in the averaged EP. The Figure shows a subtle circadian-like variation in the latency in Subject 1, which is more pronounced in Subjects 2 and 4. Interestingly, the variation can be seen in all subjects despite significant differences in the shape of the averaged EPs.

Figure 3 shows a superposition of the peak latencies for each day. The mean of the daily variation was removed before plotting the results to align the traces and reveal the trend, showing a reduction in variance at times where the drugs were taken during the day (0.33 (8am), 0.66 (4pm)). No obvious change is present at night (0 or 1 (12pm)).

IV. Discussion and Conclusion

This paper has introduced a new method for estimating excitability of brain networks. Although the data presented in this paper is rather preliminary, it is encouraging to see changes in the morphology of the EPs that are correlated with circadian cycles, and times of anti-epileptic drug delivery. This marks a step towards an implantable system for tracking and controlling pathological excitability in brain networks. Conceivably, such a system could be utilized to determine optimal therapeutic doses, and to screen potential therapies in much shorter time frames than currently possible.

A major limitation of previous studies involving intracranial EEG patients in epilepsy monitoring units has been the lack of long term data. This new system has the potential to solve this problem. Furthermore, by actively probing the brain we can selectively sample small epochs of data and efficiently track changes in brain networks, which facilitates memory management of the device.

The ability to probe the brain permits averaging of signals, which in turn allows us to extract a signal with a higher signal-to-noise ratio than what is possible from passive monitoring. Other methods exist for obtaining better information about brain networks than standard iEEG monitoring, but it

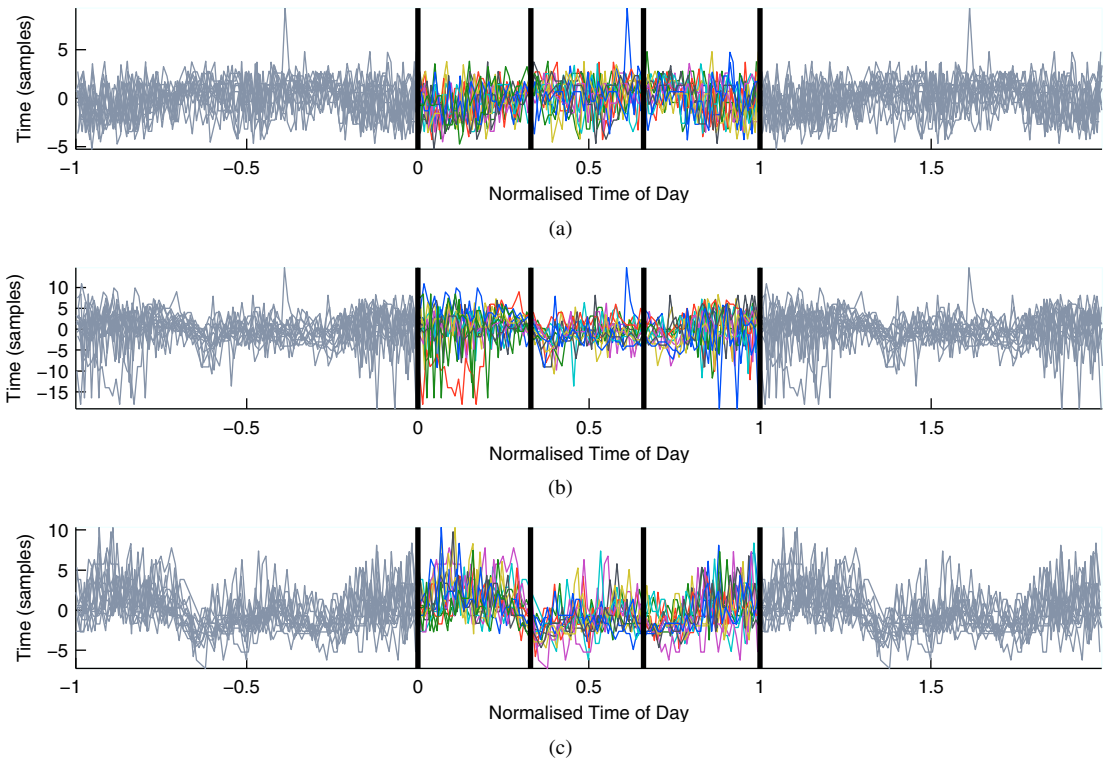

Fig. 3. Circadian Variation in the Averaged EPs. Each subfigure shows a superposition of the time to reach (mean removed) the peak of the EP for each day. The grey regions to the left and right are copies of the center colored region. The copies are shown to highlight the periodicity in the responses. The black vertical lines mark the approximate times of drug delivery. (a), (b), and (c) indicate the results are from Subjects 1, 2, and 4, respectively.

is clear that a passive feature extraction method using short-term data is not likely to solve the problem of epileptic seizure anticipation [18]. Future work will involve testing the active monitoring system on epileptic canines.

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