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Algorithm for Automatic Detection of Pentylenetetrazole-Induced Seizures in Rats

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Abstract—**Epilepsy affects approximately one percent of the world population. Antiepileptic drugs are ineffective in approximately 30% of patients and have side effects. We are developing a noninvasive, or minimally invasive, transcranial focal electrical stimulation (TFS) system through our novel concentric ring electrodes to control seizures. Here we report on the development of a seizure detecting algorithm to be used for automatic application of TFS. A cumulative sum (CUSUM) algorithm was evaluated that detected the electrographic seizure activity in all experiments well in advance of the behavioral seizure activity.**

I. Introduction

Epilepsy is a neurological disorder that affects approximately one percent of the world population with up to three-fourths of all persons with epilepsy in developing countries. [1] Over 50 million people worldwide are affected by epilepsy. Anti-epileptic drugs are ineffective in up to 30% of patients and can cause side effects. Surgery is another option available, but carries risks.

Recently electrical stimulation of the brain has shown promise in reducing seizure frequency. Implantable techniques such as the deep brain stimulation (DBS) [2-6], the responsive neurostimulator (RNS) [7, 8], and the vagus nerve stimulation (VNS) [9-13] have been widely studied.

Noninvasive forms of brain stimulation for epilepsy are gaining acceptance. There is a growing body of research on different forms of noninvasive electrical stimulation including transcranial magnetic stimulation (TMS) [14-17] and transcranial direct current stimulation (tDCS) [18]. Yet, as previously concluded by Theodore and Fisher (2004) [19] in a review of various brain stimulation techniques, the best structures to stimulate and the most effective stimuli to use are still unknown.

Previously we have shown that noninvasive transcranial focal electrical stimulation (TFS) via tripolar concentric ring electrodes (TCREs) has been effective in controlling seizures. When TFS was triggered manually after severe penicillin-induced [20, 21] myoclonic jerks there was a significant reduction in the number and length of myoclonic jerks. We also found that there was a significant reduction of the intensity of pilocarpine-induced [22] status epilepticus with the effects lasting at least hours. We recently showed that TFS significantly reduced pentylenetetrazole (PTZ)-induced hypersynchrony at the beta and gamma frequencies [23].

We also previously reported significant improvements in Laplacian electroencephalogram (EEG) recorded from human subjects with TCRE compared to EEG from conventional disc electrodes. There was a four times improvement in signal-to-noise ratio [24, 25], four times improvement in spatial resolution [25], and a ten-fold improvement in mutual information [25].

We are now developing a system which would trigger the TFS automatically based on detection of electrical seizure activity from TCREs. Seizures are usually accompanied by a significant change in the on-going electrical activity of the brain and therefore signal change detectors can be used for seizure detection. Signal change detectors, such as Shewhart, finite weighted moving average, and cumulative sum (CUSUM) [26], are traditionally used in quality control, intrusion detection, spam filtering and medical systems to identify changes in probability distribution of a stochastic random process.

Detection of seizures is challenging because: (1) there is no objective definition of what constitutes seizure electrographic activity, (2) background brain activity is non-stationary, (3) the changes introduced by seizures are non-stationary, (4) movement artifacts or non-seizure activity of the brain may resemble seizure activity, and (5) early detection, with high accuracy and specificity are required. For our seizure control system we would like to detect seizures before physical behavioral activity is observed. Therefore, we need to choose a signal change detector that is able to rapidly and reliably detect small changes and is insensitive to the probability distribution of the data. The CUSUM detector [26], fulfills these requirements, and is chosen as our change detector.

A. Basic CUSUM Detector

We first introduce the basic CUSUM detector, which determines whether a parameter θ in a probability density function (PDF) has changed. That is, to determine between two hypothesis: $H_0 : \theta = \theta_0$ and $H_1 : \theta = \theta_1$. Let p_{θ_0} and

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p_{θ_1} denote the PDF before and after the change, respectively. Let y_k denote the k^{th} sample of the data sequence (i.e. EEG segment). The basic CUSUM decision function is

$$g_k = \max(g_{k-1} + \ln \frac{p_{\theta_1}(y_k)}{p_{\theta_0}(y_k)}, 0) \quad (1)$$

$$t_a = \min\{k : g_k \geq \bar{h}\} \quad (2)$$

where $\bar{h}$ is a threshold. Here, t_a is the *stopping time*, when the detector identifies a change and raises an alarm. Each time when $g_k \geq \bar{h}$, the CUSUM detector restarts by setting $g_k = 0$ and a new round of detection begins.

When p_{θ_0} is a Gaussian process with mean μ_0, p_{θ_1} is a Gaussian process with mean μ_1, and both have variance σ^2, equation (1) detects a mean change and becomes

$$g_k = \max(g_{k-1} + (y_k - \mu_0 - \frac{\mu_1 - \mu_0}{2}), 0) \quad (3)$$

Even if the distributions are not Gaussian, the above detector is still sensitive to changes in the mean [27].

B. CUSUM Detector with Unknown Parameter

In the basic CUSUM detector, we assume that the mean value after change is μ_1. However, in practice, it is usually difficult to obtain the value of μ_1. Therefore, we use s to replace the value of $(\mu_1 - \mu_0)/2$ in equation (3), and obtain

$$g_k = \max(g_{k-1} + (y_k - \mu_0 - s), 0) \quad (4)$$

where s is a parameter of the CUSUM detector. Since the change value equals $(\mu_1 - \mu_0)$, the detector with a smaller s could be used to detect smaller changes. Therefore, the parameter s can be utilized to adjust the detection sensitivity. In this paper, we employed equation (4) for g_k as our detection function. A seizure is detected when the value of the detection function g_k goes above the threshold $\bar{h}$.

We tested the detector using the data from a previous study where TFS was applied at the first myoclonic jerk (MJ) with the goal to suppress further seizure activity. Here our goal was to demonstrate that the detector could detect a seizure before the first myoclonic jerk, the behavioral criterion used in the previous study with TFS [23].

II. METHODS

Our animal protocol was approved by the University of Rhode Island IACUC. Here, we briefly describe our experimental protocol used in the previous study when TFS was applied at the first MJ. Approximately 24 hours before the induction of seizures, an adult male 220~320g Sprague-Dawley rat was given a combination of 80 mg/kg of ketamine and 12 mg/kg xylazine (i.p) for anesthesia. The scalp was shaved and prepared with NuPrep abrasive gel (D. O. Weaver & Co., Aurora, CO, U.S.A.). Three custom-designed tripolar concentric ring electrodes [24] plus a reference were applied to the scalp using conductive paste (0.5 mm Ten20, Grass Tecnologies, RI, U.S.A.) and adhered with Teet's dental acrylic (Pearson Lab Supply, Sylmar, CA). One TCRE (10 mm), used to record from and stimulate was centered on the top of the head. Two other recording electrodes (6 mm) were placed bilaterally behind the eyes. A reference electrode was attached on the top of the neck behind the ears.

On the following afternoon the rats were placed in a transparent plastic cage and the electrodes were connected via a commutator and cables, (Plastics One, Roanoke, VA,). Skin-to-electrode impedance was measured to ensure that the impedance for the outer ring and the middle disc of electrode (1) was less than 10 KΩ. The EEG and video recording were then started. After five minutes of baseline EEG recording the PTZ was administered (55 mg/kg, ip). At the end of the experiment the skin-to-electrode impedance was rechecked. The rat behavioral activity was closely monitored and scored for seizure-related phenomena according to a scheme adapted from Mirski et al. [28]. The TFS (300 Hz, 50 mA, 200 μs, biphasic square pulses for 2 minutes) was administered when the first MJ was observed (which corresponded to the score of 3 by Racine's seizure scoring system). The control group (no TFS) rats data was used to select CUSUM parameters.

The EEG signals were preamplified (gain 100 and 0.3 Hz high pass filter) with a custom built preamplifier and then amplified using a Grass Model Neurological Research System AC amplifiers (Grass Technologies, West Warwick, RI, USA) (gain 1,000, 1.0–100 Hz, 60 Hz notch filter), and digitized (16 bits, 256 S/s). The offline CUSUM analysis and display was performed using Matlab. The two differential signals from each electrode were combined to give a Laplacian derivation as reported previously by Besio et al. [24]. Briefly, the algorithm is two-dimensional and weights the middle ring and disc difference sixteen times greater than the outer ring and disc difference.

After preprocessing, we used a 1-second long non-overlapping Hanning window (256 samples) to segment the baseline. Then the power spectrum was calculated using the FFT. The spectrum was divided into sub-bands: Delta (0.3-4Hz), Theta (4-8Hz), Alpha (8-13Hz), Beta I (13-20Hz), Beta II (20-36Hz), Gamma (36-59Hz) and high Gamma (59-100Hz). For each sub-band the spectrum was summed over frequencies and was normalized by the average baseline spectrum.

The baseline data from five control rats was used to determine μ_0 and $\bar{h}$, of the CUSUM detector. Then the parameters, μ_0 and $\bar{h}$, were set as: $\mu_0 = 1/3$ the baseline sub-band spectrum average, $\bar{h} = \mu_0 + \beta$ x(standard deviation of the sub-band spectrum) where β was manually determined for each sub-band which optimized the detection results. We tested β from 0 to 10 in 0.1 increments and found that β= 0 provided the best seizure detection rate for the 5 controls.

Parameter s was determined by adjusting s from 0 to 1000, in increments of 100, maximizing true positive (TP) and minimizing false positive (FP) rate. Therefore a compromise

value of *s* is selected for each sub-band and was kept the same for the controls (n=5) and the TFS-treated (n = 5) rat data.

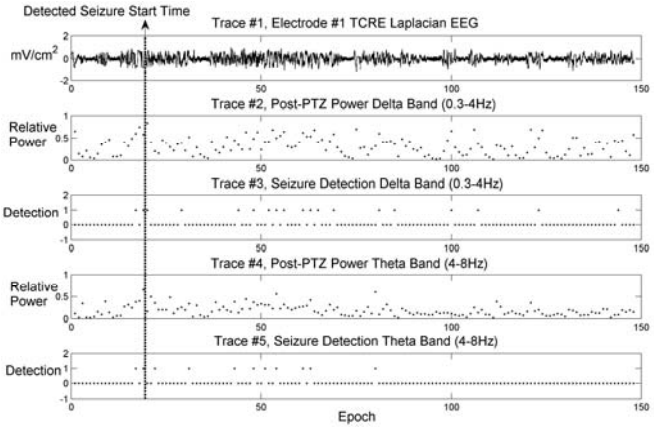

Fig. 1. Summary of the signal processing using the Delta and Theta bands power for seizure detection (Data shown for TFS rat #2.). Trace #1 is the raw EEG while traces 2 and 4 are the band powers. Traces 3 and 5 are the output of the detector. The vertical dashed line shows when the seizure was detected.

To increase the likelihood that we discriminated seizure from movement artifact we implemented a two-of-three 'seizure' smoothing algorithm. We reasoned that the seizure activity would be prolonged bursts of activity and the movement artifacts would be shorter in length.

III. Results

The data were searched and segmented manually by observing videos of the experiments, comments in the experimental log notebook, and by observing the EEG. The data were segmented into baseline (prior to giving PTZ) and post-PTZ, just after handling the rat to administer the PTZ and just prior
to the first MJ. Table 1 shows the specific times for the control and TFS-treated groups.

Fig. 1 shows a typical processed data file for a TFS-treated rat. Trace #1 is the TCRE Laplacian EEG from electrode (1). Traces #2 and #3 are the relative power and seizure detector output for the Delta band, respectively. Traces #4 and #5 are for the Theta band. The vertical dashed line shows the *stopping time* (when the seizure was detected). The first MJ was observed nearly 2 min. and 10 sec. later.

By our algorithm using Delta band power seizure was detected earlier than the first MJ in all animals of the experimental group (TFS-treated rats) with the parameter *s* determined from the control group data (rats not receiving TFS). To determine seizure onset we used a 'two-of-three smoothing' algorithm. If two out of three consecutive seizure detector outputs were 'seizure alarms' the second 'alarm' was considered as seizure onset. Table 2 shows the parameters for the CUSUM detector and the output (start epoch). There were three different *s* values used for the seven different bands.

IV. Discussion

We were able to 'train' our CUSUM detector (i.e., to select the *s* parameters) using the control rat data and apply those parameters to test the detector on data that were not used for training (the generalization property of the CUSUM algorithm). The μ_0 and $\bar{h}$ parameters were chosen from the baseline TCRE EEG for each rat via specific algorithms removing user bias of the selection. The detector determined the seizure onset in the TFS-Treated rats, on average, 79 sec. (STD 43.12 sec.) prior to the first myoclonic jerk.

Table 1. Segment times for Control and TFS rats. myoclonic jerk (MJ), administration (Admin.)

Control Rat	PTZ Admin.	Post-PTZ	First MJ
1	5:16	5:25	6:27
2	5:12	5:20	6:43
3	4:56	5:10	10:34
4	6:16	6:45	7:38
5	5:09	5:30	7:04
TFS Rat	PTZ Admin.	Post-PTZ	First MJ
1	4:55	5:10	5:50
2	5:13	5:20	7:48
3	4:38	4:50	6:11
4	5:30	5:50	7:12
5	5:52	6:05	6:50

Table 2. Parameters for CUSUM detector and results.

Rat	Band	μ_0	$\bar{h}$	*s*	start epoch
1	0-4Hz	0.0701	0.2102	0.1	7
	4-8Hz	0.0371	0.1112	0.1	6
	8-13Hz	0.0239	0.0718	0.15	8
	13-20Hz	0.0362	0.1086	0.1	13
	20-36Hz	0.023	0.069	0.3	ND
	36-59Hz	0.0241	0.0724	0.3	ND
	61-100Hz	0.1139	0.3417	0.1	4
2	0-4Hz	0.1652	0.4955	0.1	19
	4-8Hz	0.1010	0.3030	0.1	19
	8-13Hz	0.0914	0.2742	0.15	21
	13-20Hz	0.0553	0.1658	0.1	22
	20-36Hz	0.0404	0.1211	0.3	ND
	36-59Hz	0.0730	0.2190	0.3	ND
	61-100Hz	0.2121	0.6363	0.1	24
3	0-4Hz	0.1389	0.4168	0.1	6
	4-8Hz	0.1198	0.3595	0.1	ND
	8-13Hz	0.0688	0.2063	0.15	ND
	13-20Hz	0.0455	0.1365	0.1	ND
	20-36Hz	0.0722	0.2165	0.3	ND
	36-59Hz	0.0742	0.2226	0.3	ND
	61-100Hz	0.1386	0.4157	0.1	ND
4	0-4Hz	0.0362	0.1085	0.1	12
	4-8Hz	0.0492	0.1476	0.1	5
	8-13Hz	0.0430	0.1289	0.15	5
	13-20Hz	0.0388	0.1165	0.1	11
	20-36Hz	0.0376	0.1127	0.3	12
	36-59Hz	0.0371	0.1112	0.3	12
	61-100Hz	0.1165	0.3495	0.1	4
5	0-4Hz	0.1044	0.3131	0.1	13
	4-8Hz	0.0984	0.2951	0.1	17
	8-13Hz	0.0820	0.2460	0.15	ND
	13-20Hz	0.0784	0.2353	0.1	15
	20-36Hz	0.0680	0.2041	0.3	ND
	36-59Hz	0.0789	0.2368	0.3	ND
	61-100Hz	0.1400	0.4199	0.1	ND

Much work has been performed in the field of seizure detection [29-32]. For our experiments we have a special case where we know when the convulsant is given after a baseline

period. We do not need to resolve long periods of baseline activity vs. seizure activity. For these experiments we were only interested in determining when the TCRE EEG showed increased activity due to the PTZ. We did not need to discriminate False Positives, 'seizure' during baseline, only during a short period post PTZ. The rest of the data is known 'seizure' data and therefore we only had to discriminate True Positive and False Negative (no 'seizure' during 'seizure').

Although using combinations of bands may be more robust for detection our data suggest that the Delta power in the on-going EEG may be most informative in this regard. This suggestion needs further confirmation in subsequent studies.

V. Conclusion

The CUSUM algorithm, in conjunction with TCRE EEG, correctly detects seizure activity from the Delta power changes in advance of the early behavioral manifestations of a seizure (such as MJs). Therefore, this algorithm can be used as a control signal to automatically trigger TFS with the goal to prevent seizure development.

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