Seizure Suppression Efficacy of Closed-Loop Versus Open-Loop Deep Brain Stimulation in a Rodent Model of Epilepsy

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***Abstract*—We assess and compare the effects of both closed-loop and open-loop neurostimulation of the rat hippocampus by means of a custom low-power programmable therapeutic neurostimulation device on the suppression of spontaneous seizures in a rodent model of epilepsy. Chronic seizures were induced by intraperitoneal kainic acid injection. Two bipolar electrodes were implanted into the CA1 regions of both hippocampi. The electrodes were connected to the custom-built programmable therapeutic neurostimulation device that can trigger an electrical stimulation either in a periodic manner or upon detection of the intracerebral electroencephalographic (icEEE) seizure onset. This device includes a microchip consisting of a 256-channel icEEG recording system and a 64-channel stimulator, and a programmable seizure detector implemented in a field-programmable gate array (FPGA). The neurostimulator was used to evaluate seizure suppression efficacy in ten epileptic rats for a total of 240 subject-days (5760 subject-hours). For this purpose, all rats were randomly divided into two groups: the no-stimulation group and the stimulation group. The no-stimulation group did not receive stimulation. The stimulation group received, first, closed-loop stimulation and, next, open-loop stimulation. The no-stimulation and stimulation groups had a similar seizure frequency baseline, averaging five seizures per day. Closed-loop stimulation reduced seizure frequency by 90% and open-loop stimulation reduced seizure frequency by 17%, both in the stimulation group as compared to the no-stimulation group.**

***Index Terms*—Closed-loop neurostimulation, CMOS, deep brain stimulation (DBS), electroencephalograph (EEG), epilepsy, epilepsy model, hippocampus, ictal, intracerebral electroencephalograph (icEEE), integrated circuit, integrated neural interfaces, neural monitoring, neural recording, neurostimulator, open-loop neurostimulation, rat, responsive neurostimulation, rodent, seizure, seizure detection, very large scale integration (VLSI).**

I. Introduction

APPROXIMATELY 50 million people worldwide have epilepsy. Mesial temporal lobe epilepsy (MTLE) is the most common type of epilepsy and is often refractory to the conventional pharmacological treatment [1]. MTLE is characterized by predisposition to unprovoked recurrent seizures mainly originating from the hippocampus and adjacent surrounding structures [2]. Patients with this type of focal epilepsy may in some cases benefit from the epilepsy surgery. Due to the overlap of epileptogenic foci with eloquent areas (language, primary motor or visual areas) many patients cannot undergo a brain resection. As a result, approximately 30% of all patients with epilepsy continue to have disabling seizures [3].

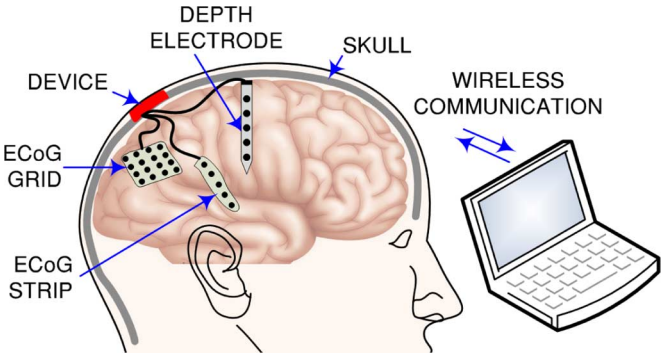

Fig. 1. Envisioned implant configuration of the proposed therapeutic neurostimulation device: neurostimulator interfaces with the ECoG grid/strip and/or the depth electrodes depending on the location of the epileptogenic zone.

Neurostimulation is an attractive alternative treatment option for patients with various neurological disorders, including refractory epilepsy. Over the last decade, two main approaches to control seizures in epilepsy have been focused on: open-loop systems, in which electrical stimulation is delivered in a preprogrammed manner independent of a patient's clinical symptoms or seizure tendency [4]; and closed-loop systems, in which stimulation is triggered in response to a seizure detection [5].

The open-loop method administers stimulation either quasi-continuously [4], [6] or intermittently (on a clock-determined cycle) [7]. Seizure occurrence patterns during day and night vary significantly, as they do from one patient to another patient and over time [8]. An open-loop system is a blind device, and no intelligent mechanism is built in to monitor brain states and tune the stimulation schedule accordingly to improve seizure control. On the other hand, a closed-loop system is generally comprised of three parts: an EEG recording system, a seizure-detecting signal processor, and a programmable neurostimulator. This system analyzes the recordings in real time and triggers a specific stimulus in response to a seizure detection [5], [9]. Fig. 1 illustrates the envisioned implanted configuration of the presented closed-loop neurostimulation device in a patient.

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The key advantages of an ideal closed-loop system over an open-loop system are: 1) high efficacy of neurostimulation—the seizure onset detector triggers the stimulation before a seizure has fully developed and is thus hypothetically easier to abort [10]; 2) a lower number of stimuli—stimulation is performed only when needed [11]; 3) fewer adverse effects—the periodic open-loop stimulation may disrupt normal brain activities [12]; 4) fewer or no battery replacement surgeries— the implanted battery life time is longer due to much fewer stimulations; and 5) the ability to review recordings to monitor the seizure frequency and to adjust parameters of seizure detection and stimulation [13], [14].

The seizure detector is a key component of the closed-loop system. As suggested, early seizure detection (before the ictal event appears) is optimal to abort an upcoming seizure efficiently. Late detection and subsequent stimulation are generally deemed as making it harder to stop the seizure [5], [15], [16]. Over the past few decades, a number of algorithms that either detect a seizure or "anticipate" it have been proposed [17]–[20]. These algorithms are usually carried out off-line using high-performance computers. These types of algorithms are generally not optimal for implementation on a low-power implantable integrated circuit (i.e., a microchip).

Advancements in the integrated circuit technology now allow for implementation of an EEG recording system, a seizure-detecting signal processor, and in some cases a programmable neurostimulator in a small and low-power implantable device. Recently, some seizure detector algorithms have been proposed for implantable applications, some with promising off-line human data results for seizure detection only [21]–[24], others with important but statistically insignificant small-scale (e.g., single-rat) animal studies, [25]–[27]. Other than the choice of the signal processing algorithm for seizure detection, another consideration is the quality of icEEG recordings, which can be improved by using low-impedance recording electrodes [28]–[30] and low-noise preamplifiers [31]–[33].

Apart from seizure detection, several other issues are important in order to achieve seizure control in epilepsy, such as optimal electrical stimulation *parameters*, *location* and *safety*. High-frequency ($>$50 Hz) and low-frequency ($<$5 Hz) deep brain stimulation (DBS) have been reported to reduce the seizure frequency in patients [13], [14], [34] and in animal models [10], [35]. The electrical stimulation has been applied to various deep brain structures, such as subthalamic nucleus, anterior nucleus of the thalamus, cerebellum, caudate nucleus, hippocampus [10], [13], [14], [34]–[36] or a specific epileptogenic zone or adjacent regions [13], [37]. The hippocampus is a common epileptogenic zone in MTLE [2], [35], [38]. The safety of the current stimulation is usually estimated using the Shannon model [39] to ensure no tissue damage [35], [36].

The stimulation current used for the epilepsy treatment is generally 10–20 folds higher than the current utilized for other functions (e.g., EEG recording and processing) [40] in an implantable neurostimulation device. An implantable device has an austere energy budget constraint and unnecessary frequent stimulation cuts its battery life shorter. The battery replacement in the implantable device is a complicated and expensive procedure [14]. Although the periodical stimulation in the open-loop method has demonstrated reasonable efficacy in managing seizures [4], it is energy-inefficient because the same large number of stimulations is provided regardless of the extent of epileptiform activity. The energy budget of such a system can be improved by stimulation only at the seizure onset to abort its formation so that no unnecessary stimulation is performed during the normal brain state. A closed-loop stimulator indeed triggers a stimulation upon a seizure onset detection. As a result of the seizure-triggered stimulation, this method provides a relatively lower number of stimulations for seizure suppression compared to the open-loop method. The closed-loop method is generally deemed as more energy-efficient as well as higher efficacy in managing seizures [37].

Both an open-loop system (Vagus Nerve Stimulator (VNS), Cyberonics, Inc., Houston, TX, USA) and a closed-loop system (Responsive Neurostimulator System (RNS), NeuroPace, Mountain View, CA, USA) have been approved by the U.S. Food and Drug Administration for the treatment of refractory epilepsy. The treatment efficacy of the VNS was demonstrated in 65 patients over more than ten years [4]. Among them, 15% became seizure-free, 90.8% of patients showed more than 50% reduction in the seizure frequency and, on average, the seizure frequency was reduced by 76.3%. The RNS trials reported approximately 20% of patients rendered seizure-free for period of six months or more, 54% of the patients experiencing a 50% or greater reduction in seizures and, on average, a 53% seizure frequency reduction in patients [37]. In academia, excellent seizure reduction efficacies in the rodent models of epilepsy have been demonstrated using open-loop (e.g., quasi-continuous [6], intermittent [41]) and closed-loop (e.g., seizure detection-triggered [9], manually triggered [35]) stimulation. To the best of our knowledge, no comparative seizure control efficacy study comparing open-loop and closed-loop stimulation in the same subject population has ever been performed.

This paper presents a long-term chronic evaluation (240 subject-days or 5760 subject-hours) of seizure control efficacy using the closed-loop and the open-loop configurations of a custom-designed closed-loop neurostimulator in the same animal group. This comparison is performed under the equal energy budget constraint in order to yield an equal implanted battery lifetime. Experimental results show that the closed-loop configuration reduced seizure frequency by 90% and the open-loop configuration reduced seizure frequency by 17%. During the closed-loop stimulation, four out of five rats in the stimulation group became convulsive-seizure-free. The closed-loop stimulation technique demonstrated several advantages over the open-loop stimulation for controlling chronic seizures.

The rest of this paper is organized as follows. Section II describes a chronic seizure model induction method, a custom-built programmable neurostimulation device, the stimulation parameters and the experimental procedure. Section III presents the effect of electrical stimulation on seizure activity in the rat hippocampus *in vivo* and compares the seizure suppression results of applying closed-loop and open-loop stimulation. Section IV describes the energy efficient stimulation method. Finally, the stimulation efficacy is compared with that of other reported methods in Section V.

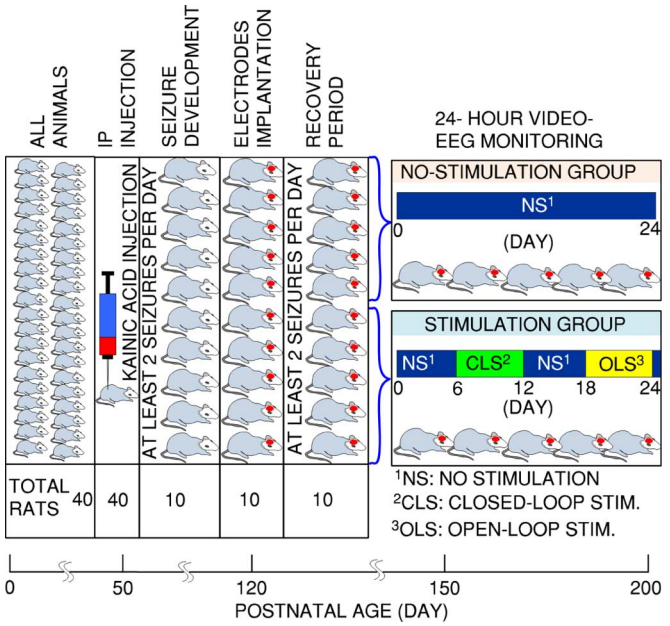

Fig. 2. Experimental procedure: 40 male Wistar rats were used in this study. Kainic acid was injected into the rats at their 50-day age and after ~60 days of injection, ten rats developed spontaneous seizure. All seizure induced rats were anesthetized for electrode implantation around their 120-day age. Later these rats were randomly divided into two groups to evaluate the seizure suppression efficacy. The no-stimulation group went through the 24-hr video EEG monitoring, but the stimulation group had four experimental phase (each phase was six days long).

II. Methods and Materials

A. Animals

A total of 40 male Wistar rats (275–400 g) were used. Fig. 2 illustrates the experimental procedure as described in the following. All the experimental procedures were conducted at The Hospital for Sick Children (Toronto, Canada) and performed according to the protocols approved by the Animal Care and Ethics Committee.

B. Chronic Seizure Induction

Kainic acid (KA, Sigma-Aldrich) was injected intraperitoneally (13 mg/Kg dissolved in saline) into the 40 rats to induce temporal lobe epilepsy. A total of ten rats had recurrent spontaneous seizures and thus were used in the remainder of this study.

C. Electrode Implantation

All ten seizure-induced rats were anesthetized with isoflurane and oxygen and placed in a stereotaxic frame (Stoelting Company, Germany). Body temperature was maintained at 37°C with a temperature controlled heating pad. The animal hair was shaved, and the skin was pretreated with atropine, lactate ringer USP and lidocaine. A small slit was created in the skin overlying the head to expose the skull. Two burr holes were drilled in the skull overlying the right and left temporal lobes [Fig. 3(a) and (b)]. Two bipolar electrodes (Plastics One, Roanoke, VA, USA) were chronically implanted bilaterally into the CA1 regions of the hippocampi using a stereotaxic

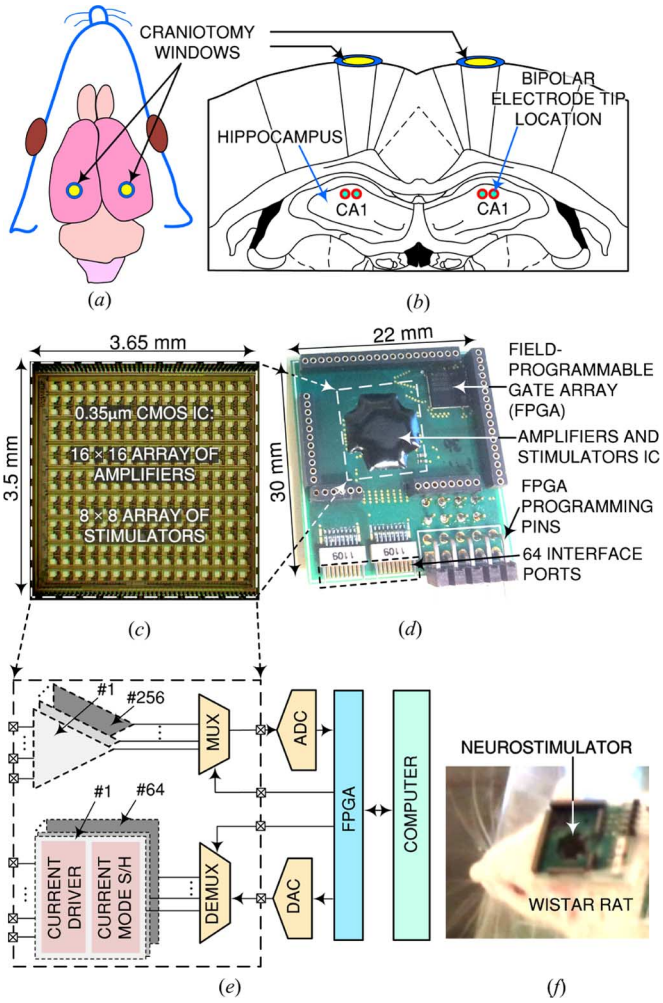

Fig. 3. Bipolar electrode implantation: (a)–(b) locations of craniotomy windows and implanted electrode tips; (c) bi-directional neural interface custom integrated circuit with 256 neural amplifiers and 64 neurostimulators; (d) custom-made programmable therapeutic neurostimulation device with 64 recording channels or 64 stimulation channels enabled; (e) system-level block diagram; and (f) a freely moving rat with the neurostimulator mounted on the head to demonstrate the form factor.

micro-manipulator, for a total of four recording or four stimulation channels (eight channels out of 128 available are utilized in this study).

D. Neurostimulator

Fig. 3(c)–(f) shows the therapeutic neurostimulation device. The neurostimulation device is a custom-built 22 mm × 30 mm PCB carrying two main components: a neuro-interface integrated circuit (chip) and a field-programmable gate array (FPGA) [36]. This neurostimulator interfaces the implanted bipolar electrodes with amplifies, and filters, processes the signals in real time, detects a seizure and triggers a programmable electrical stimulation pattern either upon a seizure onset detection (i.e., closed-loop mode) or in a periodic manner (i.e., open-loop mode).

1) *Amplifier and Stimulator*: A microchip was custom designed to provide a maximum of 256 recording and 64 stimulation channels [42]. The chip was wire-bonded onto the PCB with 64 recording channels or 64 stimulation

channels enabled and was protected by epoxy [36]. The amplifier in each recording channel has a mid-band gain programmable from 54 to 72 dB, programmable bandwidth of 1 Hz to 5 kHz with 7.99 $\mu V_{\rm rms}$ input-referred noise. The stimulation channel has a programmable current from 20 to 250 μA.

2) *Seizure Detector*: A small, low-power FPGA was also soldered to the neurostimulator PCB for controlling the neurointerface chip and performing additional signal processing. The icEEG recordings were processed in the FPGA and a computer in real time to trigger responsive neurostimulation for suppressing seizures. This seizure detection algorithm is based on the detection of the reduction in the magnitude of the synchrony index [43], [44]. The phase synchrony index is defined as $R = | < e^{i\Delta\theta} > |$, where $\Delta\theta$ is the phase difference between the two hippocampal recordings [45].

E. 24-Hour Video-EEG Monitoring

Following the electrode implantation, the rats were placed in electrically screened Plexiglas chambers. The implanted electrodes were connected to the responsive neurostimulator for icEEG recording and hippocampus neurostimulation. Continuous icEEG recordings were acquired at 10 ksps using the neurostimulator, for 24 hours a day, for 24 days. The behavior of the animals was also video-recorded simultaneously with the icEEG recording.

F. Electrical Stimulation Parameters

The stimulation consisted of bipolar monophasic current (amplitude of 150 μA) pulses (pulse width 100 μs) delivered to the hippocampus at 5 Hz for 5 seconds at a time. The stimulation charge per phase (the area of the electrode pad is 12 000 μm^2) was set to be three times lower than the maximum deliverable charge in order to avoid tissue damage [35], [36], [39].

G. Neurostimulation Experimental Procedure

Fig. 2 (right) depicts the neurostimulation experimental phases. All ten implanted rats were randomly divided into two groups: 1) no-stimulation and 2) stimulation. In the no-stimulation group (five rats), seizures were monitored and labeled by the responsive neurostimulator and cross validated using the video recordings. The seizure frequency per day was determined during 24 days. The stimulation group (five rats) went through four experimental phases for the evaluation of seizure suppression efficacy of the closed-loop and open-loop stimulation: i) no stimulation; (ii) closed-loop stimulation; (iii) no stimulation; and (iv) open-loop stimulation. During the first phase, seizures in the stimulation group were monitored only (similar to the no-stimulation group). Next, in the second phase, the responsive neurostimulator was turned ON to trigger a stimulation upon a seizure precursor detection. The average number of feedback stimulations per day in the stimulation group was quantified. The same number of stimulations was used in the open-loop stimulation phase (phase four), but in a periodic manner (at equal intervals). Phase three, a no-stimulation phase in between the closed-loop and open-loop stimulation phases was used to re-evaluate the seizure frequency baseline.

H. Statistical Data Analysis

The following statistical measures were employed to evaluate the seizure detection performance and the treatment efficacy.

True positive (TP): a correct seizure onset detection; *false positive* (FP): a false seizure onset detection; *true negative* (TN): a correctly rejected non-epileptic event; *false negative* (FN): a missed seizure onset detection.

Sensitivity: the ratio of the number of TPs to the total number of TPs and FNs.

Specificity: the ratio of the number of TNs to the total number of TNs and FPs.

Statistical tests were done in Matlab (Mathworks) using the Statistics Toolbox. Results are expressed as the mean $\pm$ the standard deviation (STD). The level of significance was set to $p < 0.05$.

III. Results

As stated, 10 rats out of 40 developed chronic, spontaneous seizures one to two months after a kainic acid injection. These rats were used for the experiments. They were assigned randomly to the no-stimulation and the stimulation groups, five rats each. The no-stimulation group members had 4.92 seizures per day on average or a total of 591 seizures in the 24 days of experiments. The behavior associated with seizures was scored according to the modified Racine scale of 0 to 5 (0—behavioral arrest, motionless, hair raising, excitement and rapid breathing; 1—mouth movement of lips and tongue, vibrissae movements and salivation; 2—head clonus and eye clonus; 3—foreline clonus, wet dog shakes; 4—clonic rearing; and 5—clonic rearing with loss of postural control and uncontrollable jumping) [46].

Fig. 4(a)–(c) illustrates the synchrony index R calculated for (a) normal brain activity; (b) a seizure; and (c) during closed-loop perturbation that aborted a possible seizure in the stimulation group. In the baseline/normal EEG [Fig. 4(a)], R fluctuated mostly between 0.4 and 0.6. Fig. 4(b) shows that R dropped rapidly down to 0.2 preceding an ictus (i.e., a seizure), and increased to over 0.7 during the seizure (Racine scale for the seizure behavior was 4 and 5).

Fig. 5 illustrates the seizure precursor detection sensitivity and specificity for these ten rats. The overall sensitivity and specificity of the detection were 94.16% and 85.62%, respectively. The average time for early seizure onset detection was 53.64 $\pm$ 47.96 s before the electrographic seizure onset. A total of 297 seizures were recorded behaviorally and electrographically from the two groups, and all the events were cross validated using video-icEEG recordings. The device detected 94.11% (279 of 297) of all seizures with 0.67 $\pm$ 0.59 false alarms per day.

The accurate seizure precursor detection ensures proper stimulation timing. For example, Fig. 4(c) depicts the closed-loop stimulation (5 Hz for 5 s) once the R has dropped sharply to 0.2. Subsequently, after the stimulation, no seizure behavior was observed. The absence of seizure activity after the stimuli represents a seizure abortion.

The no-stimulation group had on average 4.95 seizures per day [Fig. 6(a)] in the first 14 days of experiment. Rats

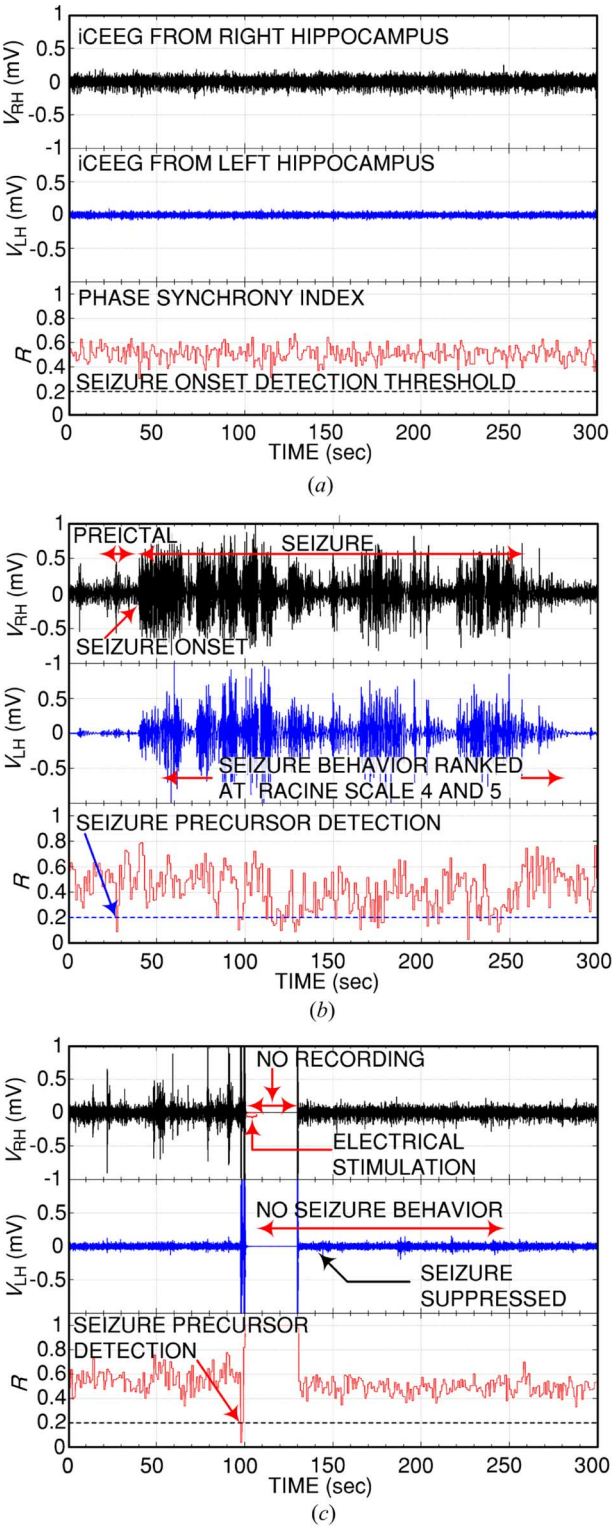

Fig. 4. Phase synchrony index (R) variations for the normal baseline EEG, seizure and seizure suppression recordings using the neurostimulator. V_{RH} is EEG signal from the right hippocampus and V_{LH} is the EEG signal from the left hippocampus, R is the synchrony index between V_{RH} and V_{LH}. (a) Basal (interictal) EEG recordings and the corresponding PLV. (b) Electrographic seizure recordings and seizure onset detection using R. (c) Automatic seizure onset detection, self-triggered electrical stimulation, and subsequent seizure suppression.

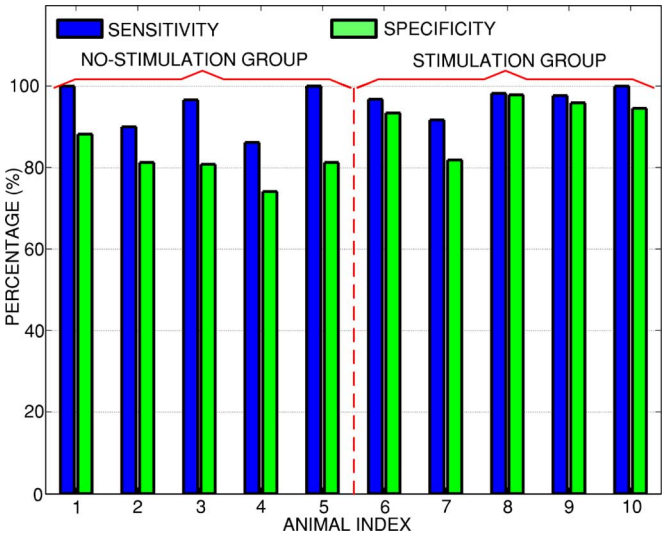

Fig. 5. Seizure precursor detection performance: seizure onset detection performance based on 297 seizures from the no-stimulation group (five rats) and from periods of no stimulation in the stimulation group (five rats).

in the stimulation group had a similar baseline seizure frequency average as the no-stimulation group, at 5.00 and 5.83 seizures per day (without stimulation) before the open-loop [Fig. 6(b)] and closed-loop [Fig. 6(c)] stimulation, respectively. Fig. 6(b) shows the average seizure frequency of 4.1 seizures per day during the open loop stimulation, which correspond to a 18% reduction in the number of seizures. Once the stimulator has been turned off at the end of the open-loop stimulation phase, the seizure frequency went back up (4.5 seizures per day in the days after the open-loop stimulation stage, implying minor post-stimulation inhibition). In the closed-loop stimulation phase [Fig. 6(c)], the rats received a stimulation upon a seizure precursor detection and the seizure frequency dropped to 0.5 seizures per day on average, which corresponds to a 91% reduction in the number of seizures. The stimulator was turned off at the end of the closed-loop stimulation phase and the seizure frequency went back to the level of 4.95 seizures per day. During the closed-loop stimulation, four out of five rats became convulsive seizure free.

The number of closed-loop stimulations was, on average, 11 $\pm$ 5.2 per day. This average number of stimulations was used in the open-loop stimulation phase, but in the latter case the stimuli were not associated with the detection of the precursor but occurred in a periodic manner (equal intervals). For example, if the closed-loop stimulation phase had 11 stimulations per day on average, the following open-loop stimulation would schedule one stimulus (identical to that of the closed-loop stimulation: 5 s at 5 Hz) every 130 minutes.

The stimulation parameters used in this study ensured that the delivered charge was three times lower than the maximum allowed delivered charge per phase in Shannon model [39]. Thus, no tissue damage due to the stimulation was observed in the histology analysis.

IV. Energy Efficient Stimulation

One of our objectives of this study was to determine optimal utilization of the electrical stimulation energy source (e.g., an implantable battery) for the best seizure suppression. The

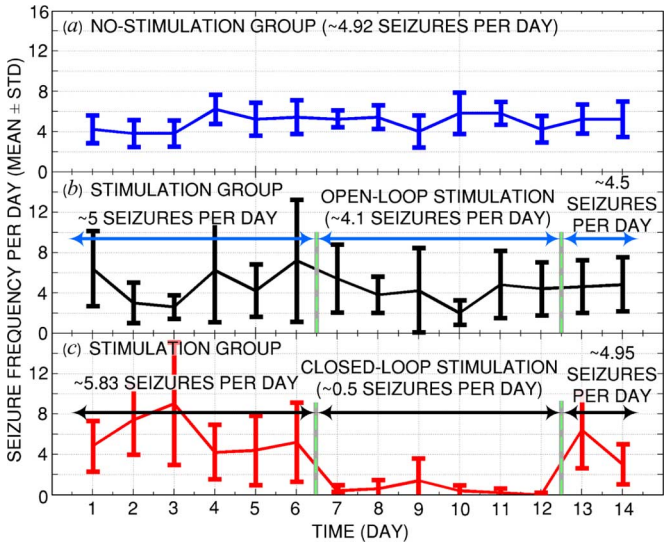

Fig. 6. Seizure frequencies in the no-stimulation and stimulation groups: (a) no-stimulation group had 4.92 seizures per day on average, (b) the open-loop stimulation reduced the seizure frequency by 18%, and the closed-loop stimulation reduced the seizure frequency by 91%. The seizure frequency during the closed-loop stimulation phase was reduced significantly compared to the no stimulation phase, open-loop stimulation phase and no-stimulation group ($p < 0.05$).

number of stimulations is a critically important issue in the implantable battery-powered therapeutic systems. Generally in an implantable device, the power used for sensing and signal processing is low compared to the stimulation power. Thus the battery lifetime is mainly dependent on the number of stimulations and its parameters. As previously stated, in this study, the optimal number of stimulations was determined for the best seizure suppression using the closed-loop stimulation method. The same number of stimulations was then used in a periodic fashion in the open-loop stimulation. The seizure suppression efficacy of the two methods was thus compared on the basis of the equal energy budget.

Fig. 7 illustrates a 24-day seizure and stimulation diary of a rat in the stimulation group, and each subfigure represents an experimental phase: a) no stimulation; b) closed-loop stimulation; c) no stimulation; and d) open-loop stimulation phases. In the no-stimulation phase (six days), this rat had five seizures per day on average and the presented neurostimulation system detected 33 of 35 seizures (94% sensitivity) with four false alarms in six days (86% specificity). This rat had a higher seizure tendency around midnight [Fig. 7(a)].

In the closed-loop phase (six days) shown in Fig. 7(b), the rat had only two undetected seizures [false negatives in Fig. 7(b)]. The neurostimulator had only four false alarms (in six days) caused by the abnormal movement artifacts (confirmed by the video recording). The stimulation record shows frequent stimulations around midnight, which correlates well with seizure temporal distribution in the no-stimulation phase [Fig. 7(a)]. Overall, the neurostimulation device triggered on average 11 stimulations per day (sometimes two stimulations were required for one seizure abortion), and 0.33 seizures per day were observed, which correspond 93% reduction in the number of seizures.

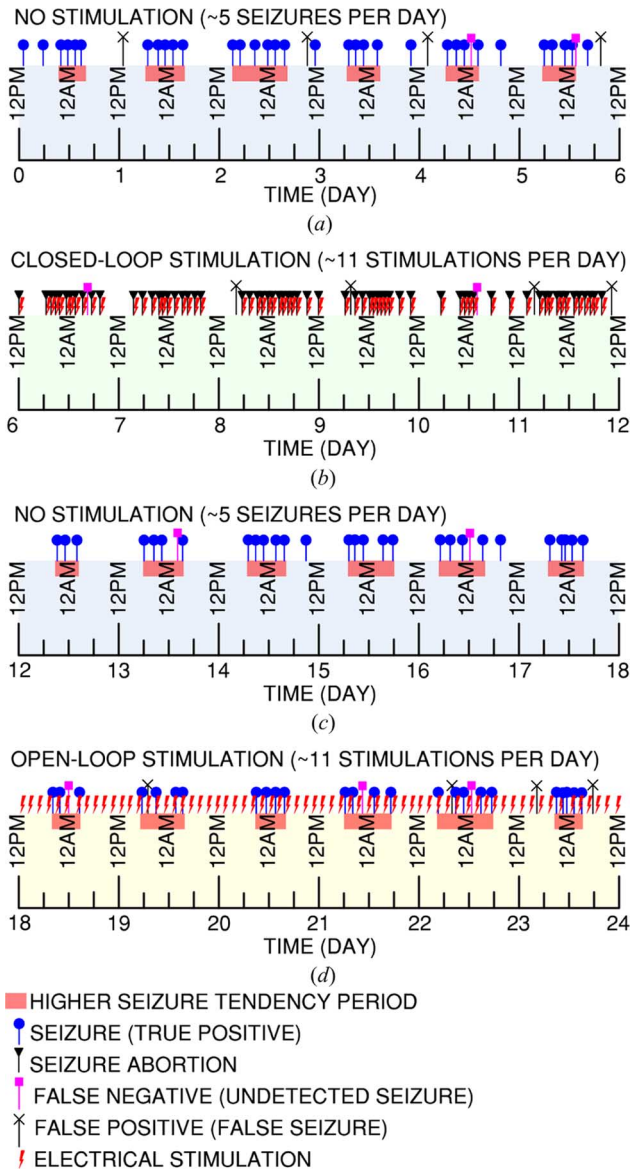

Fig. 7. The 24-day seizure and stimulation record of one rat in the stimulation group including four 6-day experimental phases: (a) no stimulation, (b) closed-loop stimulation, (c) no stimulation, and (d) open-loop stimulation.

In the third phase, another 6-day no-stimulation phase shown in Fig. 7(c), which comes after ending the closed-loop stimulation phase, the seizure frequency returned to the baseline level of approximately five per day. Similar to the previous no-stimulation phase, most of the seizures were observed around midnight. Next, the average number of stimulations per day of 11 counted during the closed-loop stimulation phase was used in a periodic manner during the open-loop stimulation phase. This corresponds to triggering one stimulation every 131 minutes [Fig. 7(c)]. During this phase, seizure rate was slightly reduced to 4.1 per day from the average 5 at baseline, which represents an 18% reduction in seizure frequency. As occurred in previous [Fig. 7(a)–(c)] no-stimulation phases, Fig. 7(d) shows that most of the seizures during this phase were observed around midnight. Thus, there were many unnecessary stimulations during the daytime when the seizure tendency was lower, but not enough stimulations at midnight when the

TABLE I
COMPARATIVE SEIZURE SUPPRESSION STUDY OF CLOSED-LOOP AND OPEN-LOOP DEEP BRAIN STIMULATION IN RODENT MODELS OF EPILEPSY

Reference		Lado [47]	Takebayashi et al. [41]	Rashid et al. [6]	Rajdev et al. [35]	Good et al. [9]	Krook-Magnuson et al. [48]	This work	
Method		Open-loop	Open-loop	Open-loop	Closed-loop	Closed-loop	Closed-loop	Open-loop	Closed-loop
Stimulation parameters	Location	Anterior nucleus of the	Anterior nucleus of the	Ventral hippocampal	Hippocampus	Centromedial thalamic nuclei	Hippocampus	Hippocampus	Hippocampus
	Current	200 μA	320 μA	200 μA	150 μA	400 μA	Optogenetic	150 μA	150 μA
	Pulse width	100 μsec	100 μsec	100 μsec	240 μsec	100 μsec	N/A	100 μsec	100 μsec
	Frequency	100 Hz	130 Hz	1 Hz	5 Hz	130 Hz	N/A	5 Hz	5 Hz
	Duration	30 sec	30 min	60 min	5 sec	1 min	N/A	5 sec	5 sec
	Triggers per day	92	24	19	N/A	N/A	N/A	~11 per day (periodic)	~11 per day (responsive)
Seizure suppression rate		50%	56.9%	90%	Shorten the seizure duration	>50%	29.6%	17%	90%
Projected battery life (QL0700I simulated)		4 months	<1 month	15 months	N/A	N/A	N/A	428 months or > 35 years	428 months or > 35 years

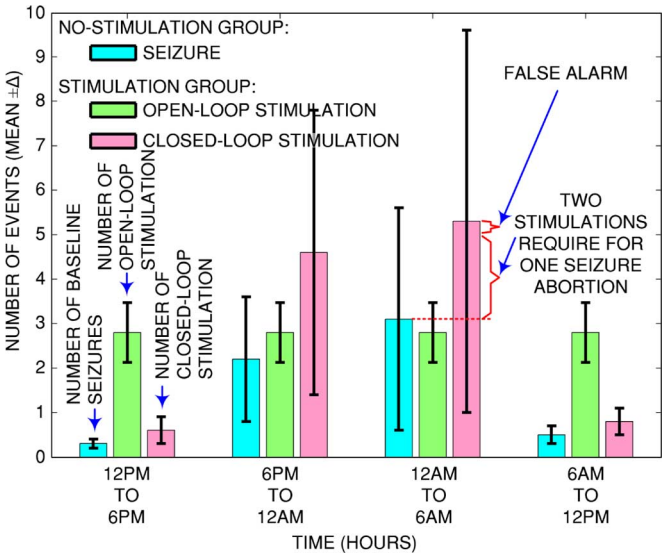

Fig. 8. Average seizure number per rat in the no-stimulation group and the average stimulation number per rat in the stimulation group. The no-stimulation group exhibited higher seizure frequency during the night and early morning, but lower seizure frequency during the day. In the stimulation group, the closed-loop stimulation method triggered a higher number of stimulation during the higher seizure tendency periods (e.g., 12 AM to 6 AM and 6 PM to 12 AM), but lower stimulation during the lower seizure tendency periods (e.g., 6 AM to noon and noon to 6 PM). The open-loop stimulation method delivered the same number of stimulations during the day and night regardless of the seizure tendency.

seizure tendency was higher, due to the suboptimal periodic nature of the stimulation.

Similar seizure suppression results were revealed in the other rats in the stimulation group. Fig. 8 depicts the seizure frequency and the stimulation frequency average of all seizure-induced rats in the no-stimulation and stimulation groups during four 6-hour time periods of a day. Fig. 8 illustrates that the no-stimulation group demonstrated higher seizure frequency during the 6 PM to 12 AM (~2.5 seizures) and 12 AM to 6 AM (~3 seizures) time intervals, but lower seizure frequencies (~0.5) during the daytime. Fig. 8 shows that the closed-loop stimulation method triggered a higher number of stimulations (~5) during the higher seizure tendency periods and lower (~0.6) during the lower seizure tendency periods. The open-loop stimulation method delivered the same number of stimulations (2.8) during the day and night regardless of the seizure tendency. Overall, the seizure frequency was reduced by 90% by the application of closed-loop stimulation while the open-loop stimulation resulted in only 17% reduction.

The state-of-art demonstrated similar 90% seizure suppression using an open-loop method by the application of quasi-continuous stimulation (60 min ON and 15 min OFF) in a rodent model of epilepsy [6]. In an implantation configuration, this quasi-continuous stimulation would deplete the battery quickly and shorten the battery lifetime. However, the presented closed-loop method suppresses 90% seizure frequency using 11 ± 5.2 stimulations per day (total stimulation time $= 55$ s in 24 hr), which would deplete the battery 331 times slower rate than the open-loop study [6].

V. DISCUSSION

The main goal of this study was to determine the seizure suppression efficacy using two common electrical stimulation methods in the same rats with chronic seizures under an equal energy budget. Our work reveals better seizure suppression efficacy and several advantages of the closed-loop stimulation over the open-loop stimulation. For comparison with other DBSs reported, Table I summarizes results of other closed-loop and open-loop DBS in rodent models of epilepsy. Our study featured 90% and 17% seizure suppression using the closed-loop and open-loop stimulations, respectively. Also, the stimulation paradigm used in this study was of a relatively brief duration and with a lower intensity compared to other studies. As a result, the forecasted battery life of the implant is approximately 35 times higher than that in the existing studies.

A. Stimulation Parameter Adjustment

An open-loop system is relatively a simple device, which has a scheduled stimulation pulse generator. The clinician often adjusts the open-loop stimulation parameters based on the patient seizure frequency over some periods. This blind tuning process

(without off-line analysis of the stored icEEG recordings) requires much iteration before reaching the patient-specific optimal stimulation parameters. On the other hand, a closed-loop system features physiological signals sensing, storing, abnormal signal rhythms detection, and stimulating upon a seizure detection. The stored icEEG recordings can be further analyzed offline to understand the clinical symptoms/biomarkers or underlying disease and adjust the seizure detection criteria and stimulation parameters for the best seizure reduction. These tuning parameters improve early seizure state detection and subsequent seizure abortion using a minimal stimulation.

B. High Efficiency of Closed-Loop Stimulation

High and low frequency DBS have been reported to reduce seizure frequency in epilepsy. High frequency (130 Hz) stimulation has resulted as well in shorter seizure latency and propagation [49]. Specifically, low frequency stimuli in the range 0.5 to 5 Hz has been reported to reduce significantly the seizure frequency in patients [34] and animal models [10], [35]. Low-frequency stimulation may be advantageous over high-frequency due to fewer current pulses and subsequently lower risk of tissue damage. The presented closed-loop system detects the seizure onset rapidly and triggers a brief stimulation (parameters: amplitude $=$ 150 μA, frequency $=$ 5 Hz and duration $=$ 5 s) before the ictal event fully develops. The effect of this brief stimulation disrupts seizure development completely and brings back the normal brain state. The stimulation parameters used in the closed-loop stimulation resulted in 90% seizure frequency reduction compared to the seizure frequency baseline in no-stimulation phases of the stimulation and no-stimulation groups. In contrast, the open-loop stimuli reduced only 17% seizure frequency because their periodic stimuli were not associated with an impending seizure rather continuous depolarization or hyperpolarization of neurons [6] (details in Section V-D).

C. Number of Stimulations and Battery Lifetime

The stimulation current (e.g., 150 μA) is relatively large compared to the current dissipation for other processing (e.g., 1.36 μA) in an implantable device. A closed-loop method triggers a stimulation as per seizure onset detection, while an open-loop method provides a quasi-continuous stimulation (e.g., 60 min ON, 15 min OFF [6]). Simulation results showed that the quasi-continuous stimulation (e.g., [6]) depletes an implantable Lithium ion battery (QL0700I) in 1.25 years; however, the $\sim$11 closed-loop stimulations per day depletes the same battery slower rate that lasts for 35 years.

D. Less Adverse Effects

The optimal number of stimulations for the best seizure suppression is desirable for a longer battery life as well as lower possible adverse effects. State-of-the-art open-loop stimulation methods normally implement a quasi-continuous or intermittent stimuli for the seizure control. These current pulses have been proposed to depolarize or hyperpolarize cells such that ictal events are less favored to develop. At the same time, these quasi-continuous periodic perturbations may disrupt other physiological rhythms [50]. The closed-loop stimulation provides stimulation as required or upon abnormal icEEG pattern detection; whereas the open-loop stimulation delivers the same level stimulation in a periodic manner regardless of the extent of icEEG recording. The presented study demonstrates an optimum number of closed-loop stimulations by using a higher number of stimulations during higher seizure tendency periods and a lower number of stimulations during lower seizure tendency periods. This automatic tuning mechanism prevents unnecessary stimulation during the normal brain state.

VI. Conclusion

This study demonstrates engineering aspects associated with the effective epileptic seizure control and proposes a therapeutic neurostimulation device for the treatment of refractory epilepsy. The results of this study using a custom-built therapeutic neurostimulation device reveal a greater efficiency at reducing ictal events (90% seizure frequency suppression) using a closed-loop stimulation method, whereas the open-loop resulted in a 17% reduction. This seizure suppression efficacy is achieved as a result of triggering a stimulation just before a seizure development, in response to an abnormal icEEG pattern detection; whereas the open-loop system delivers stimulations periodically. Thus, the closed-loop strategy increases efficiency of the stimulations, while reducing the possible side effects using the minimum number of stimulations as required. Therefore, an effective alternative to the open-loop neurostimulator is the closed-loop neurostimulator, in which the involvement of deep brain stimulation is minimal. As an extension of the work on epilepsy, the new era of deep brain stimulation strategies based on closed-loop paradigms may be able to target different pathological aspects of brain activity for the treatment of various neurological disorders.

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