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A bidirectional brain-computer interface for effective epilepsy control*

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Abstract: Brain-computer interfaces (BCIs) can provide direct bidirectional communication between the brain and a machine. Recently, the BCI technique has been used in seizure control. Usually, a closed-loop system based on BCI is set up which delivers a therapic electrical stimulus only in response to seizure onsets. In this way, the side effects of neurostimulation can be greatly reduced. In this paper, a new BCI-based responsive stimulation system is proposed. With an efficient morphology-based seizure detector, seizure events can be identified in the early stages which trigger electrical stimulations to be sent to the cortex of the brain. The proposed system was tested on rats with penicillin-induced epileptic seizures. Online experiments show that 83% of the seizures could be detected successfully with a short average time delay of 3.11 s. With the therapy of the BCI-based seizure control system, most seizures were suppressed within 10 s. Compared with the control group, the average seizure duration was reduced by 30.7%. Therefore, the proposed system can control epileptic seizures effectively and has potential in clinical applications.

Key words: Brain-computer interface, Epilepsy, Seizure detection, Responsive neurostimulation
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1 Introduction

Epilepsy is a chronic neurological disorder affecting 50 million people worldwide. Epileptic seizures usually cause convulsions, loss of consciousness, and muscle spasms that shadow the patients' lives. Currently, available treatments for epilepsy patients include pharmacotherapy and surgical resection. Despite their effectiveness, over one third of patients are refractory because of drug-resistance or because they are in an inappropriate condition for surgery (Kwan and Brodie, 2000; Engel *et al.*, 2003). A promising choice for these patients is neurostimulation that delivers electrical current to neural tissue for treatment. Although neurostimulation of epileptogenic foci has been proven as an effective method to alleviate epileptic seizures (Velasco *et al.*, 2007; Fisher *et al.*, 2010; Berényi *et al.*, 2012), the conventional stimulation protocol, which gives stimulation continuously or according to a predefined schedule, has not been widely applied due to its side effects and the high damage caused to the tissue.

The rapid progress achieved in brain-computer interface (BCI) technology makes it feasible to

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construct effective neurostimulation systems with low side effects (Motamedi *et al.*, 2002; Morrell, 2011). BCI aims to provide a bidirectional communication pathway between the brain and a machine (Pfurtscheller *et al.*, 1993; Wolpaw *et al.*, 2000; 2002) and has shown great potential in motor function rehabilitation (Velliste *et al.*, 2008; Hochberg *et al.*, 2012). An integrated BCI-aided neurostimulation system, i.e., responsive stimulation system, can detect seizures automatically by identifying epileptic discharges, and trigger neurostimulation as a feedback application. Instead of stimulating the tissue in predefined protocols, such a BCI-aided therapy delivers neurostimulation only when seizure occurs; therefore, the side effects of electrical stimulation can be noticeably reduced (Kossoff *et al.*, 2004; Rosin *et al.*, 2011).

There is growing evidence that BCI-based systems for responsive stimulation can provide safe and effective treatment for epilepsy in both animals and humans (Velasco *et al.*, 2001; Vonck *et al.*, 2002; Kinoshita *et al.*, 2005). Psatta (1983) constructed a closed-loop system that delivered low-frequency stimulation (5 Hz) in response to seizure onset. Animal experiments showed that better spike suppression performance was achieved by responsive stimulation than by random stimulation, which indicated the effectiveness of the responsive system. Osorio *et al.* (2005) reported a responsive system that suppressed seizures with high-frequency stimulation (100–500 Hz). The system showed the strength of seizure blockage in an experiment involving eight patients. Wang *et al.* (2012) proposed another responsive seizure control system that uses low-frequency stimulation (1 Hz) for seizure suppression in rats. Compared with stimulation in an open-loop manner, the responsive system achieved lower seizure frequencies and shorter seizure durations.

Although the BCI-based systems have shown some capacity for seizure suppression, the optimal parameters for responsive stimulation remain unclear. Motamedi *et al.* (2002) evaluated the seizure terminating effects of neurostimulation with different parameters. Results showed that stimulations became most effective in after-discharge suppression if they were delivered early. Sun *et al.* (2008) also noted the importance of early detection and stimulation. This led to the development of an implantable responsive neurostimulation system (RNS) which recently received Food and Drug Administration (FDA) pre-market approval (Morrell, 2011). The small device can detect seizures in real time and deliver therapy stimulations ranging from 1 to 333 Hz, which could be tuned patient-specifically. The success of RNS revealed the great potential of responsive stimulation systems. However, the optimal parameters for responsive stimulation can be affected by a lot of factors including the model, stimulation sites, timing, and differences between patients (Bikson *et al.*, 2001; Kinoshita *et al.*, 2005; Wang *et al.*, 2008). Since the underlying mechanism controlling the effect of electrical stimulation on seizure suppression is still unknown, how these factors influence stimulation parameters remains unclear (Kinoshita *et al.*, 2005; Velasco *et al.*, 2005). Therefore, responsive stimulation systems need to be studied further for both research purposes and clinical applications.

In this paper, we propose a new BCI-based responsive stimulation system for epilepsy control. Our system includes a signal amplifier, a seizure detector, a neurostimulator, and a software platform to provide integrated control. To detect seizures in the early stages, we propose the use of a morphology-based spike identification algorithm for seizure identification. This method can detect seizure events in real time with short delays, to trigger early stimulation for seizure suppression. The system was tested on rats with penicillin-induced epileptic seizures. In our system, 83% of the seizures were detected successfully with a short time delay of 3.11 s. With the responsive cortical stimulation, the average seizure duration reduced by 30.7%. Results show that our responsive simulation system can control epileptic seizures effectively. This work can be seen as a preliminary study of cyborg intelligence (Wu *et al.*, 2013), which connects biological and machine intelligence for a specific purpose.

2 Materials and methods

2.1 Animals and surgery

Adult male Sprague-Dawley rats were used in the experiment (250–350 g, Grade II, Certificate No. SCXK2003-0001, Experimental Animal Center, Zhejiang Academy of Medical Science, Hangzhou, China). The rats were anesthetized with 1% pentobarbital sodium (60 mg/kg) administered intraperitoneally, and mounted on a stereotactic apparatus. A midline incision was made along the scalp to expose the skull. To access the cortical signal, holes were drilled into the skull and stainless steel screw recording electrodes (0.3 mm in diameter) were implanted. A total of four electrodes were implanted for signal acquisition and cortical stimulation: two placed over the frontal cortex, 2 mm anterior to the bregma (LF and RF), and two placed over the parietal cortex, 2 mm posterior to the bregma (LP and RP) (Fig. 1). Reference and ground electrodes (RO and LO, respectively) were placed in the bone over the cerebellar cortex in symmetrical positions against the midline (AP: 10.5 mm, L: 1.5 mm). Before electrode LP was implanted and connected to the socket, penicillin (5 μL, 400 IU) was injected 2.3 mm below the skull at 1 μL/min through a microsyringe. The needle was not removed until 5 min after injection. The duration of the surgery was limited to no more than 2 h.

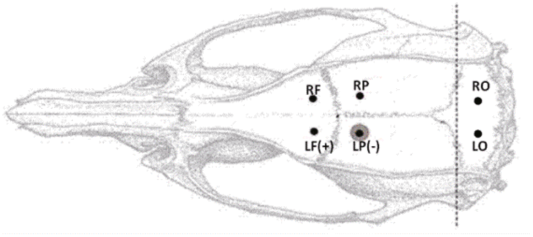

Fig. 1 Placement of cortical electrodes. Four screw electrodes (LF, RF, LP, and RP) are used for cortical signal recording and the stimulations are delivered from LF to LP. The LO and RO are used as ground and reference electrodes, respectively

2.2 BCI system for responsive stimulation

The responsive stimulation therapy was delivered by a bidirectional BCI system. The system includes three parts, a signal acquisition system as the input, an automatic seizure detector as the control, and a current-controlled stimulator as the output. As the signals are acquired and recorded, the automatic detection program works in real time to identify seizure events as early as possible. Once a seizure is detected, the stimulator generates and delivers an electrical stimulus with predefined parameters to suppress the ongoing seizure. A diagram of the system is illustrated in Fig. 2.

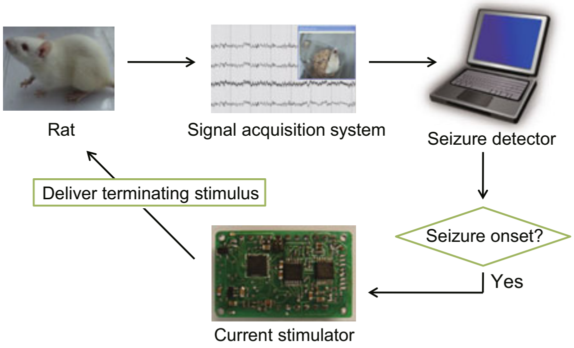

Fig. 2 Diagram of the BCI-based responsive stimulation system. The BCI system has three main components: a signal acquisition system as the input, a seizure detector as the control, and a current-controlled stimulator as the output. A stimulus is triggered once a seizure is detected

2.2.1 Software

The BCI system is controlled by a software program. The software system serves as an integrated controller that links the signal recorder, seizure detector, and stimulator together to perform responsive stimulation. The software receives brain signals from the NeuroScan system with a TCP socket and displays the waveform in real time (Fig. 3). The behavior of the rat was recorded synchronously by a video camera. As the signals are acquired and recorded, the seizure detection program runs to identify seizure events. When a seizure is detected, the system sets off an alarm and triggers a cortical stimulus with serial port commands. The software integrates useful functions such as signal recording, display controlling, and channel montage setting. It also provides an easily accessible user interface to configure the parameters for seizure detection and stimulation. The software program is implemented in C#.

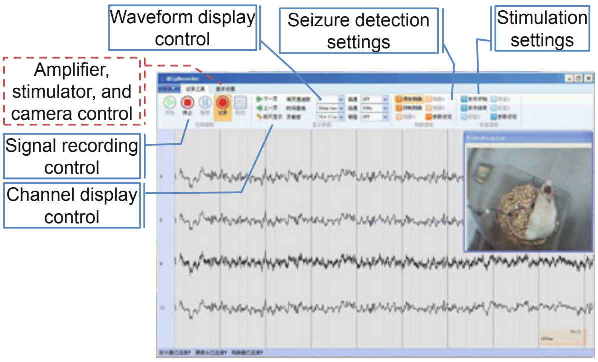

Fig. 3 User interface of the software program

2.2.2 Hardware

The hardware equipment in the BCI system includes a multichannel signal amplifier and a neurostimulator. We used the Nuamps system (Neuroscan, USA) to acquire cortical electroencephalography (EEG) signals from the rats. For the neurostimulator, we have developed a multichannel stimulation system to deliver current-controlled pulses to the cortex of the brain. The neurostimulator contains three main parts, a C8051 microprocessor-based controller, a constant-current generator, and a serial communicator (Fig. 4). The neurostimulator communicates with the computer via a serial port. Once a command is received from the computer, the controller translates the command into stimulation parameters and controls the constant-current generator to output a corresponding stimulus. The neurostimulator has two independent channels. Each channel can be configured to deliver square waves ranging from 1 to 1000 Hz, current amplitudes from 0 to 12.5 mA, and pulse-widths from 0.1 to 2.5 ms.

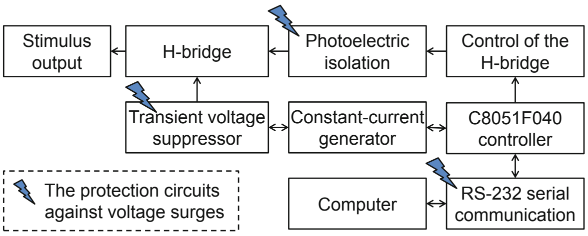

Fig. 4 System diagram of the neurostimulator. The neurostimulator receives serial commands from the computer, and outputs a corresponding stimulus. Protection modules were designed for safety reason

2.2.3 Real-time seizure detection

Four channels of cortical EEG signals LF, RF, LP, and RP are recorded. The sample rate is set to 500 Hz and a band-pass filter spanning DC to 200 Hz is applied at acquisition.

The seizure detector aims to detect seizure events from cortical EEG signals in the early stage. Since most epileptic activities are characterized by closely-spaced spikes or slow waves (Mormann *et al.*, 2007; Carney *et al.*, 2011), we designed a seizure detector to identify seizures automatically by recognizing such patterns. In the proposed system, we use a morphology-based spike identification method for efficient seizure detection. A flowchart of the seizure detection process is illustrated in Fig. 5.

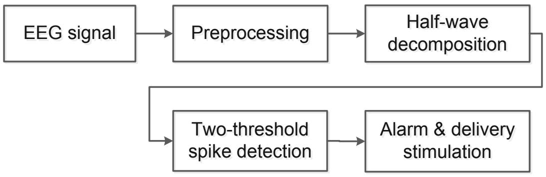

Fig. 5 Flowchart of the real-time seizure detection method

1. Preprocessing. Before spike detection, preprocessing procedures including segmentation and baseline removal are applied. Firstly, the continuous cortical brain signals are segmented into time windows by a sliding window of 1 s with a stride of 1 s. Then the baseline of each time window is estimated using least squares linear fitting. The baseline is then subtracted by the original time window to minimize the effects of signal drift.

2. Half-wave decomposition. Half-wave decomposition is an effective procedure for time domain spike feature extraction (Grewal and Gotman, 2005). For each time window, we first locate all the local maxima and local minima, and then we connect each adjacent maximum and minimum to obtain a half-wave sequence. Short half-waves are removed for smoothing. A half-wave set with N elements is defined as

$$\{w_i\}_{i=1}^{N}, w_i = (t_i, \max_i, \min_i, \mathrm{dir}_i), \tag{1}$$

where w_i is a half-wave with a four-dimensional property: t_i denotes the timestamp of the ith half-wave, $\max_i$ and $\min_i$ the maximum and minimum values of the half-wave respectively, and dir_i the direction of the half-wave ($\mathrm{dir}_i = 0$ if the slope of the half-wave is negative, and $\mathrm{dir}_i = 1$ otherwise).

3. Two-threshold spike detection. For the half-wave set $\{w_i\}_{i=1}^{N}$, we identify spikes with a two-threshold method. A spike is characterized according to the following criteria:

(1) A spike should begin with a half-wave w_i and end with a half-wave w_j where $\mathrm{dir}_i = 0$ and $\mathrm{dir}_j = 1$.

(2) For both w_i and w_j, $\max_i$ and $\max_j$ should be above $\mathrm{TH}_{\mathrm{high}}$ and $\min_i$ and $\min_j$ should be below $\mathrm{TH}_{\mathrm{low}}$.

(3) The time difference between t_i and t_j should be no larger than $\mathrm{TH}_{\mathrm{span}}$.

A time window is regarded as an abnormal window if it contains more than $\mathrm{TH}_{\mathrm{count}}$ spikes. A seizure is detected if more than $\mathrm{TH}_{\mathrm{window}}$ abnormal windows appear successively.

2.2.4 Responsive stimulation

The stimulus is delivered using the two electrodes, LP (anode) and LF (cathode). During the stimulation, the seizure detection function pauses to avoid false alarms caused by stimulation artifacts. After stimulation, the system will re-detect epileptiform activity and another therapy will be triggered if epileptic discharge is still detected.

3 Results and discussion

Experiments were carried out to test the performance of the proposed system for seizure suppression. First, the seizure detection performance of the spike identification method was evaluated, and then the effect of seizure suppression of the proposed system was assessed and analyzed.

3.1 Experiment setup

A total of 16 rats were randomly divided into two groups. The rats of the first group (stimulation group) received responsive stimuli with the BCI system; the second group (control group) served as a control group that received no stimulation. For both groups, video-EEG monitoring of each rat started 1 h after the penicillin injection and lasted six consecutive hours. In the experiment, there were a total of 96 h of cortical EEG data with 4024 seizures. All the data were used for evaluation, without selection.

To obtain optimal seizure detection and suppression performance, preliminary experiments were carried out for setting parameters. For seizure detection, both $\mathrm{TH}_{\mathrm{high}}$ and $\mathrm{TH}_{\mathrm{low}}$ were obtained by cross-validation methods with eight rats; for stimulation, experiments were carried out with 30 rats to select the best stimulation frequency among 1 Hz, 60 Hz, and 100 Hz. The parameters of the BCI system used in this experiment are given in Tables 1 and 2.

3.2 Seizure detection performance

To evaluate the seizure detection performance, three commonly used criteria of sensitivity, specificity, and detection time delay (TD) were employed. Sensitivity is defined by the proportion of seizures detected; TD refers to the absolute time difference between the timestamps of true seizure and detection by the system. The timestamps of seizures were visually labeled by two independent examiners and the average results were used; for specificity, we used Yadav's definition (Yadav *et al.*, 2012), which is the proportion of true positives among the seizures detected by our method.

The results show that the morphology-based spike identification method in the BCI system could efficiently identify seizure events within short time delays. On average, 83% of the seizures were detected successfully within a detection time delay of 3.11 s. The detection results of all eight rats in the stimulation group are shown in Table 3. High sensitivities of 81%–95% were achieved for the first seven of the eight rats. However, for the 8th rat, a relatively low detection rate was obtained due to short-term seizure onsets (a lot of seizures with durations of less than 3 s). For the 5th and 7th rats, the specificities were below 60%, which indicates high false alarm rates. For both rats, false alarms were triggered mostly by artifacts during electrode failure. For the first seven of the eight rats, the average TD for each was less than 4 s. Such quick detection can

Table 1 Parameter configurations for seizure detection

Parameter	Value	Parameter	Value
Channel	LP	$\mathrm{TH}_{\mathrm{span}}$	300
$\mathrm{TH}_{\mathrm{high}}$ (μV)	−200	$\mathrm{TH}_{\mathrm{count}}$	3
$\mathrm{TH}_{\mathrm{low}}$ (μV)	−300	$\mathrm{TH}_{\mathrm{window}}$	2

Table 2 Parameter configurations for positive square wave stimulation

Parameter	Value	Parameter	Value
Pulse width (μs)	300	Current (μA)	100
Frequency (Hz)	100	Duration (s)	2

Table 3 Seizure detection results

Rat	Sensitivity	Specificity	Time delay (s)
1	0.84	0.79	3.43
2	0.95	0.60	2.70
3	0.81	0.72	3.68
4	0.81	0.64	3.27
5	0.86	0.56	2.26
6	0.91	0.89	2.66
7	0.85	0.55	2.42
8	0.57	0.91	4.45
Average	**0.83**	**0.71**	**3.11**

trigger therapy stimulations in the early stages of seizure to give effective seizure suppression.

An experiment was carried out to compare the seizure detection performance of our BCI system with that of other seizure detectors. Two fast online seizure detection methods were carefully implemented for comparison. The first was line-length (Sun *et al.*, 2008), which is defined as the average of absolute sample-to-sample differences within a window; the second was the differential windowed variance (DWV) (Majumdar and Vardhan, 2011), which is calculated as the variance of the differentiation of a window.

The seizure detection results of the competitor methods were obtained in a pseudo-online manner, and the time window was set to 1 s with a stride of 1 s (Table 4). Compared with the line-length detector, our method achieved a significantly higher detection rate ($p < 0.05$, paired t-test, null hypothesis). Although the sensitive line-length method had a shorter time delay, more false alarms were triggered. Compared with the DWV method, our proposed detector achieved a similar average detection delay with a significantly higher detection rate ($p < 0.05$, paired t-test, null hypothesis). Although the average specificity of the DWV method was higher than that of our method, the difference was not significant ($p > 0.05$, paired t-test, null hypothesis). Overall, superior performance was achieved by our proposed method. Since spike-like-patterns are typical of epileptic signals, the straightforward spike detector should detect most seizures with short delays. Therefore, it could trigger stimuli effectively in response to seizures.

Table 4 Seizure detection comparison

Method	Sensitivity	Specificity	Time delay (s)
Line-length (Sun *et al.*, 2008)	0.67 ± 0.14	0.60 ± 0.20	2.40 ± 1.09
DWV (Majumdar and Vardhan, 2011)	0.64 ± 0.12	0.80 ± 0.10	3.30 ± 0.97
Our method	0.83 ± 0.11	0.71 ± 0.14	3.11 ± 0.74

3.3 Seizure suppression performance

In this section, we evaluate the seizure suppression performance of the BCI system. First, we present the seizure control results of our proposed system in comparison with the control group, and then the results are analyzed to explore further the effects of responsive neurostimulations.

3.3.1 Seizure suppression results

The effect of responsive stimulation was assessed using two criteria: average seizure duration and total seizure count. All seizure events were identified and labeled by visual inspection of the cortical signals. The minimum duration and spike frequency that characterized a seizure were defined as more than 2 s and at least 2 Hz, respectively. For each seizure event, the start and end points were marked by two independent examiners and the average results were used. The time interval between the start and end of a seizure event was considered as the seizure duration.

The results of seizure suppression are illustrated in Table 5. For the control group, the mean seizure duration time was 14.61 s. With the responsive stimuli, the average seizure duration time reduced to 10.12 s, which was 30.7% lower than that of the control group ($p < 0.05$, independent t-test, null hypothesis). In addition, all eight rats in the control group had average seizure durations above 10 s, while only three rats in the stimulation group had mean durations longer than 10 s. The total number of seizures in the stimulation group was higher than that of the control group. This result is acceptable since the parameter of seizure count can vary widely among different individuals. Therefore, the responsive cortical stimulation system effectively suppressed seizures by reducing their duration.

In Fig. 6, we illustrate examples of seizure suppression resulting from the use of our proposed system for three different rats in the stimulation group. Shortly after onset, the seizures were detected by the system, and then stimulations were triggered. In all

Table 5 Seizure suppression results

Rat	Count		Duration (s)	
	Stimulation group	Control group	Stimulation group	Control group
1	277	147	8.71	13.24
2	207	288	9.70	21.52
3	168	106	10.22	14.60
4	289	268	7.89	18.43
5	271	277	9.43	10.60
6	363	103	14.06	13.99
7	309	144	9.16	11.86
8	602	205	11.80	12.65
Average	**310.8**	**192.3**	**10.12**	**14.61**

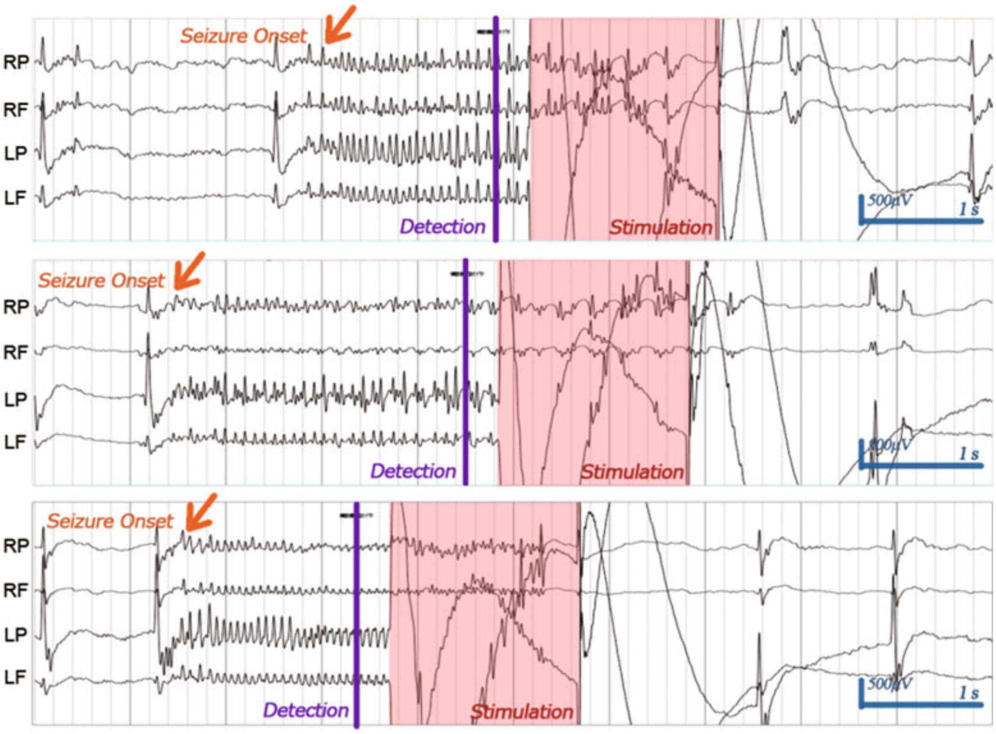

Fig. 6 Examples of seizure suppression results with responsive stimulation. In each subgraph, four channels of cortical signal are recorded. LP and LF were used for stimulation and LP for seizure detection. Shortly after onset (orange arrow), seizures were identified by the detector (purple line) and stimuli were delivered (red block). The short interval between detection and stimulation was due to the hardware delay of the stimulator. For all three different rats in the stimulation group, the seizures aborted before the stimulations ended. References to color refer to the online version of this figure

three cases, the responsive stimuli aborted the ongoing seizures effectively.

3.3.2 Statistical analysis

Statistical analysis was carried out to explore further the effects of responsive stimulation. First, we analyzed the seizure duration distribution of the stimulation group and the control group. We divided seizure durations into five bins (0–8, 8–12, 12–16, 16–20, and >20, unit: s), and drew a histogram for each group. In the stimulation group, the electrical stimuli showed seizure abortion effects so that the seizure durations were notably reduced (Fig. 7). About 54% of seizures were aborted within 8 s, while in the control group, the proportion was only half of that. Moreover, more than half of the long-term seizures (longer than 16 s) were reduced. These results indicate that responsive cortical stimulation suppresses ongoing seizures effectively.

We also analyzed the relationship between stimulation and seizure abortion (Fig. 8). That is, the proportion of seizures terminated during the stimulation or within a few seconds after stimulation. For two of the eight rats, more than 30% of seizures terminated during stimulation (0 on the horizontal axis), and for seven of them, this proportion was above 20%. Overall, 42%–64% of seizures stopped within 2 s after stimulation. These results strongly

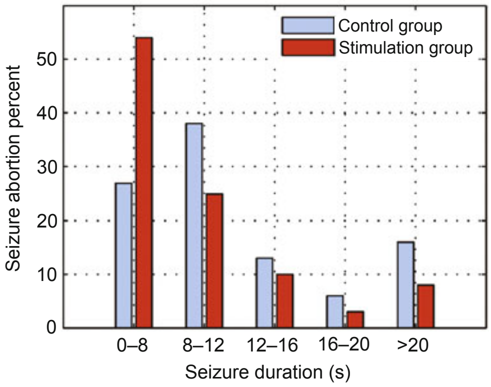

Fig. 7 Distribution of seizure duration in the stimulation and control groups. The seizures have been divided into five bins according to their durations

confirm the inhibitory effects of responsive stimulation on seizures.

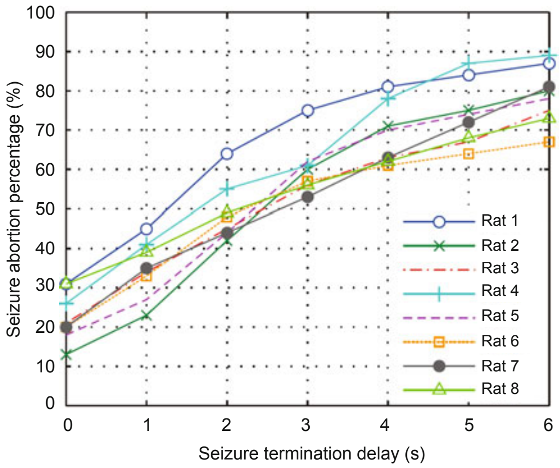

Fig. 8 The relationship between stimulation time and seizure abortion time. The horizontal axis indicates the time after stimulation, and the vertical axis represents the percentage of seizures stopped within that time. The 0 s on the horizontal axis denotes seizures aborted before stimulation ended

4 Conclusions

In this study, we developed a BCI-based responsive stimulation system for effective suppression of seizures. With the efficient morphology-based spike identification method, seizures could be recognized accurately within a short time to trigger therapy stimulations in the early stages of onset. Experimental results showed that the responsive seizure suppression system could abort ongoing seizures effectively.

Compliance with ethics guidelines

All experiments were carried out in accordance with the ethical guidelines of the Zhejiang University Animal Experimentation Committee and were in complete compliance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

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