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REVIEW ARTICLE

Neural Signal Processing for Closed-loop Neuromodulation

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Abstract
Purpose The purpose of this article is to provide an overview of the current status of neural signal processing techniques for closed-loop neuromodulation.
Methods First we described overall structure of closed-loop neuromodulation systems. Then, the techniques for the stimulus artifact removal were explained, and the methods for neural state monitoring and biomarker extraction were described. Finally, the current status of neuromodulation based on neural signal processing was provided in detail.
Results Closed-loop neuromodulation system automatically adjusts stimulation parameters based on the brain response in real time. Adequate tools for signal sensing and signal processing can be used to obtain meaningful biomarkers reflecting the state of neural systems. Especially, an appropriate neural signal processing technique can optimize the details of stimulation for effective treatment of target disease.
Conclusions Neural signal-based biomarkers reflecting the pathophysiological statuses of patients are essential for closed-loop neuromodulation, and they should be developed from an understanding of the relationship between clinical states and neural signals.

Keywords Closed-loop neuromodulation, Neural signal processing, Deep brain stimulation, Treatment, Biomarker, Local field potential, Single unit activity

INTRODUCTION

Neuromodulation systems can provide restoration of brain function or recovery from neurological/psychiatric diseases by modulating the nervous system, primarily using electrical stimulation [1, 2]. It has been proven as an effective means for the recovery from disorders such as Parkinson's disease (PD) [3], dystonia [4], obsessive-compulsive disorder [5], tremor [6, 7], chronic pain [8, 9], and post-traumatic stress disorder [10].

Neuromodulation system can be classified into an open-loop or a closed-loop system. Conventional neuromodulation systems are open-loop, in which the parameters for the stimulation are fixed, whereas the stimulation parameters are varied in closed-loop systems based on the state of the patient in real-time [2, 11, 12]. Closed-loop systems are expected to improve outcomes of neuromodulation, minimize side effects and lower cost compared to conventional open-loop systems [11].

To date, closed-loop neuromodulation techniques have been applied to several neurological diseases. In PD patients, dynamic feedback control of stimulation triggers provided substantial improvement of motor symptoms [13]. Biomarkers for pain extracted from brain activities are used to deliver electrical stimulation to suppress pain perception in neuropathic disease [14]. Seizure onset was detected from neural signals, which were used to trigger electrical stimulation to prevent seizure propagation in epilepsy patients [15].

Closed-loop neuromodulation can be represented by a block diagram shown in Fig. 1. The essential blocks are neural signal sensing and signal processing to obtain meaningful biomarkers, which can be defined here as a quantitative measure derived from the neural signals, reflecting the instantaneous state of the patients. The biomarkers should reflect the severity of the disease. Understanding the pathophysiological properties of the relevant disease is crucial. The location of the stimulation and recording is determined from the relevant neurophysiological knowledge.

The methods for the neural signal recording include single-unit activity (SUA), local field potential (LFP), electrocorticogram (ECoG) and electroencephalogram (EEG). The recorded neural signal is transformed into disease-specific biomarkers. Each disease is characterized by its own neurophysiological property, and neural signal processing

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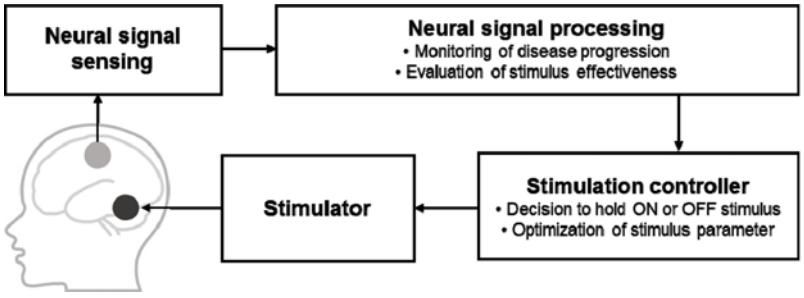

Fig. 1. A block diagram of feedback control in closed-loop neuromodulation.

strategies should be devised accordingly. For example, PD patients show decreased beta rhythm and cross-frequency coupling between beta- and broad-band activities in the motor cortex [16]. In epilepsy patients, the seizure onset zone was effectively detected by analyzing inter-regional functional connectivity between cortical areas [17]. The signal processing block should be carefully devised so that the effectiveness of the stimulation can be evaluated and/or the state of neural systems can be monitored.

The stimulation controller updates the details of current stimulation pulses based on the result of neural signal processing for the biomarker extraction. Adjustable stimulation control is necessary considering individual differences and time variance of neural systems. For example, an adjustable stimulation control can use a recursively identified autoregressive model of the correlation between stimulation input parameters and dynamically extracted biomarkers [18]. The output of the stimulation controller provides the stimulator with detailed stimulation parameters such as frequency, pulse width and current/voltage amplitude.

Neural signal processing is essential for the optimization or adjustment of the parameters and the decision of stimulation onset/offset. If necessary, artifact removal algorithms should be applied to recover neural signal from severe contamination by stimulation artifacts. More importantly, the state of neural systems, including the severity of disease, should be estimated from neural signals. This estimation requires methods for the extraction of disease-specific biomarkers by neural signal processing.

The purpose of this review is to introduce neural signal processing techniques for closed-loop neuromodulation systems, including stimulation artifact removal and neural state monitoring. We also provide a detailed overview of the current status of applying neural signal processing to closed-loop neuromodulation for several neurological disorders.

SIGNAL PROCESSING TECHNIQUES FOR STIMULUS ARTIFACT REMOVAL

To organize a feedback loop effective for functional restoration by closed-loop neuromodulation, it is necessary to observe the dynamic changes of biomarkers, which are evoked by electrical stimulation. However, simultaneous electrical stimulation with neural recording induces a stimulation artifact in recorded neural signals. There is significant spectral contamination between the neural signal and the stimulation artifact. Therefore, stimulus artifact removal strategies are required for reliable extraction of neural signals. In this section, we introduce several neural signal-processing strategies to obtain clear neural activities by removing stimulation artifacts.

A common method for stimulation artifact rejection is interpolation. Stimulation artifacts were removed by replacing the sample points at each stimulus artifact event with a value interpolated along a straight line that was computed from neighboring sample points [19, 20]. For example, after detection of the stimulus artifact event time using an amplitude threshold level, interpolation of the artifact duration between the beginning and the end of the artifact sample and exponentially decaying tail was performed [20]. Advantages of the interpolation method are better conservation performance of the spectral component in the neural signal and better computational efficiency than other currently available artifact rejection methods. However, interpolation methods commonly cause distortion or removal of neural spiking information during the artifact pulse duration.

Alternatively, to minimize the distortion of the action potential during the stimulus pulse duration, the template subtraction method was applied [21, 22]. For example, a template subtraction method of Wichmann [21] was based on assuming the shape of the stimulus artifact by estimating of the average stimulus artifact, which was calculated from traces of multiple stimulations at the recording sites. Gathered artifact shapes were averaged and subtracted from individual segments that contained the stimulus artifact. The main advantages of the template method are that it is highly effective for stimulus artifact removal while preserving neuronal signals and that it allows a more precise investigation of the changes in neuronal activity during electrical stimulation. One of the primary limitations of the template subtraction method is that it is difficult to match the artifact template to

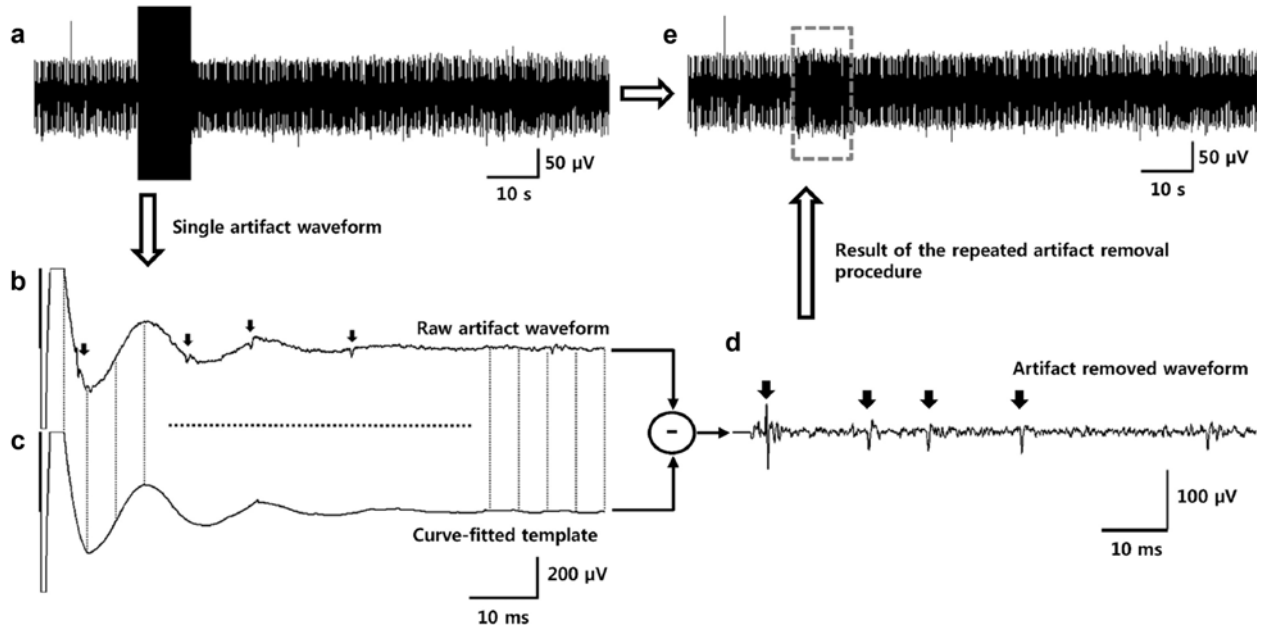

Fig. 2. Protocol for artifact removal with a curve-fitting method with permission from ref. [23], copyright The Korean Physiological Society and The Korean Society of Pharmacology. (a) Single unit activities are covered by large stimulus artifact waveforms. (b) An example of one artifact waveform at a stimulation frequency of 10 Hz. Several spikes were mixed in the fluctuation generated by an artifact waveform (indicated by arrows). (c) The artifact waveform is divided into several segments, and each segment is curve-fitted with a 2nd to 4th order polynomial. Every curve-fitted waveform is gathered together to construct a template for artifact subtraction. (d) Spike waveforms were clearly revealed after artifact subtraction (the template is subtracted from the original waveforms). (e) The artifact waveform is divided into several segments, and each segment is curve-fitted by polynomials (2^{nd} to 4^{th} order). These curve-fitted segments are gathered to construct the artifact template, which is to be subtracted from the contaminated waveform.

individual artifact waveforms because of variation in each residual artifact. Consequently, this method may induce fluctuations that remain after template subtraction.

Curve fitting techniques can be used to overcome the side effects of fitting an artifact template to each artifact waveform [23, 24]. Here, the artifact waveform is divided into several segments, and each segment is curve-fitted by polynomials (2^{nd} to 4^{th} order) [23] (Fig. 2). These curve-fitted segments are gathered to construct the artifact template, which is to be subtracted from the contaminated waveform. Consequently, the curve fitting method enables removing residual artifact due to the variation in each stimulation artifact. However, curve fitting is computationally intensive and thus may be less effective for an implantable device.

Al-ani and colleagues suggested the ensemble empirical mode decomposition (EEMD) method for a computationally efficient artifact removal [25]. EEMD possesses some of the limitations associated with the techniques previously used to remove stimulus artifact. The main characteristic of this approach is that the neuronal signal without stimulation artifacts is reconstructed directly by eliminating the intrinsic mode functions corresponding to the stimulus artifact dynamics that are generated by the EEMD algorithm.

Generally, software-based artifact removal is limited by power consumption for computational requirements [26]. Therefore, for an effective implantable device, hardware-based artifact removal techniques may be better suited. Several hardware-based artifact removal techniques were developed so far, such as hardware blanking [27, 28], hardware filtering [29], stimulator output stage [30] and a combination of these methods [31-33]. When stimulus artifacts cannot be completely removed using hardware, various forms of software-based method may be adopted.

NEURAL STATE MONITORING AND BIOMARKER EXTRACTION

Several neurological diseases, such as PD, epilepsy and chronic pain, have their own neural characteristics, and these can be used to extract biomarkers for closed-loop neuromodulation from neural signals. To satisfy disease-specificity, these biomarkers should not only reflect the neural characteristics of the clinical status but also be easily detectable and robust during neural recording. In implantable devices, there should be no transformation or damage to the sensor during a long-term implantation, so that it can provide the biomarkers continuously under low signal-to-noise ratio (SNR) conditions [34, 35]. Extracellular recording signals or ECoG/EEG can be used as suitable candidates for extracting biomarkers in a

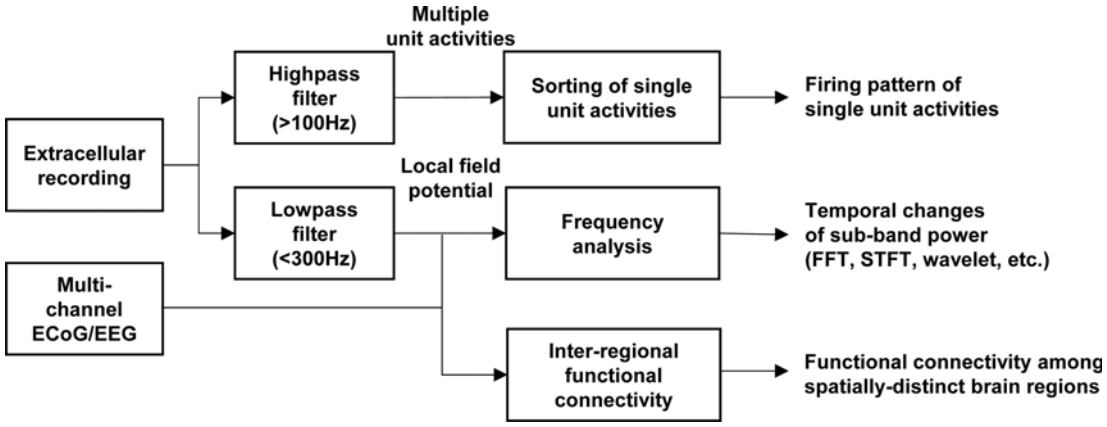

Fig. 3. Schematic diagram of neural signal processing for biomarker extraction.

closed-loop neuromodulation system. Considering idiopathic neural characteristics in different neurological diseases, we can select a suitable measurement method and extract disease-specific biomarkers from neural signals representing severity of a disease.

Single-unit/multi-unit activities: neural spike trains

SUA is a temporal pattern of a neuron's action potentials that is acquired from extracellular recording in the focal brain area. It has been widely used in various neurophysiological research studies, and it also can be used for a closed-loop neuromodulation system. However, because a few SUAs within up to 50 μm from the electrode sites are recorded, a meticulous control for selecting recording sites is necessary [36]. Glial cells may grow around the electrodes due to injury during insertion, which may deteriorate the SNR [37].

Fig. 3 shows the structure of signal processing for extracting characteristics of neural activity. Highpass filtering (> 100 Hz) is applied to an extracellularly recorded neural signal to extract the SUA. The filtered neural signal contains multiunit activity (MUA) from the neurons close to the electrode. If SNR is high enough, spikes can be easily detected based on a threshold value by thresholding. The multiunit neural signals can be sorted into single unit neural activities by extracting features that characterizing the waveforms of each single unit and classifying them using a pattern recognition technique [38, 39]. The obtained SUA may be expressed as time-varying firing rate of single neurons.

Local field potential (LFP)

LFP reflects synchronous activity of local neuronal populations and is derived from extracellularly recorded signal. The oscillatory activities of different frequency bands in LFP may contain different physiological information [40]. As Fig. 3 shows, LFP is acquired from extracellular recordings by lowpass filtering (< 300 Hz). Different diseases may have different oscillatory properties, and these differences make it feasible to obtain disease-specific neural activities from LFP. Thus they can be utilized for a closed-loop neuromodulation system. Furthermore, LFP may be better suited for a chronically implanted neuromodulation system because LFP can be recorded and analyzed by implanted electrodes for a long time [34]. Most importantly, because LFP represents the ensemble of the activities of thousands to millions of neurons around the electrode, issues such as tissue encapsulation or micromotion can be avoided, compared to the SUA. Therefore, LFP recording is robust for chronic in vivo recording [32, 41].

Spectral analysis is frequently used for the LFP analysis, in order to investigate various rhythms within the signals. This method includes discrete and fast Fourier transform (DFT/FFT), short-time Fourier transform (STFT), wavelet transform, and parametric spectrum estimation. From DFT the magnitude and phase spectra of discrete-time signal are obtained. Temporal evolution of the spectra is acquired by STFT. The procedure for STFT consists of division of a long-term signal into shorter segments and then to computing the DFT separately on each shorter segment. Wavelet transform is a method that solved a fundamental problem of STFT—the dependence of frequency resolution on the length of the time window.

ECoG and EEG reflect the activities of cortical neurons. ECoG electrodes are placed on the surface of cerebral cortex, whereas noninvasive EEG electrodes are placed on the scalp. Since the electrodes are placed on the surface of the cortex or scalp, it is difficult to record neural signals from deep structures of the brain. Epilepsy is a good candidate for closed-loop neuromodulation using ECoG or EEG. The focus of epileptic activity may be localized from seizure-related neural activities, which are recorded by multichannel electrodes covering a broad area. It is also possible to predict epileptic seizure onset from neural signals and thus can be utilized for closed-loop neuromodulation [42]. Various

Table 1. Studies on closed-loop neuromodulation/stimulation systems (see text).

Application	Recording (area)	Stimulation (area)	Feedback mechanism	Subject in experiment	Reference
PD	SUA (GPi, M1), accelerometer	DBS (GPi)	abnormal GPi or M1 spike detection	primate model of PD	[45]
PD	LFP (STN)	DBS (STN)	Beta-band (13–30 Hz) amplitude	human	[47]
Epilepsy	LFP (hippocampus)	DBS (hippocampus)	afterdischarge potentials	sheep	[26, 33]
Epilepsy	ECoG or depth leads (seizure onset region)	DBS (Seizure onset region)	line length, area under the curve and half-wave decomposition	human	[56]
Epilepsy	LFP (amygdalohippocampal regions)	DBS (seizure onset regions or anterior thalami)	Energy burst detection at 5–45 Hz	human	[50]
Epilepsy	ECoG/LFP	Cortical stimulation	abnormal phase synchrony of cortical signals	rats (online), humans (offline)	[43]
Epilepsy	SUA&LFP (frontal and parietal cortical areas)	TES (temporal or frontal midline electrodes on the skull)	when spike-and-wave episodes were detected	rats	[49]
Pain	SUA (spinal cord)	DBS (PAG)	firing rate of SUA	rats	[68]
Pain	SUA (spinal cord)	DBS (VTA)	firing rate of SUA	rats	[69]
Neurogenic bladder	SUA (spinal cord sensory nerves)	Electrical stimulation (Spinal cord)	firing rate of SUA correlated with bladder filling	rats	[70]
Neural prosthesis after spinal cord lesion	LFP (M1, PMd), EMG	Electrical stimulation (spinal cord ventral horn)	amplitude of LFP of 90–160 Hz or EMG above threshold	non-human primate	[71]
Paralysis after stroke	ECoG or EEG (M1)	Cortical stimulation (M1)	spectral power in the μ/β band	human	[72]
Performance test	SUA (S1)	Cortical stimulation (M1)	triggered by neural spikes discriminated on the adjacent electrode in S1	rats	[73]

neural processing techniques can be applied for the epileptic biomarkers based on ECoG or EEG including temporal waveform characterization, spectral analysis, inter-regional connectivity [43, 44] or cross-frequency coupling [16].

CURRENT STATUS OF CLOSED-LOOP NEUROMODULATION USING NEURAL SIGNAL PROCESSING

Table 1 summarizes the literature on closed-loop neuromodulation which utilizes neural signal processing for active adjustment of stimulation.

Parkinson's disease (PD)

PD is a slowly progressing neurological disease characterized by tremor, rigidity, and sluggish movement. It is commonly treated by dopamine agonist levodopa in initial treatments. It is not unusual that the medication become ineffective as the disease progresses, and surgery to implant stimulation electrodes has been performed. In fact, the PD is one of the most well-known neurological disorders that can be treated by electrical stimulation, specifically deep brain stimulation (DBS). Many disease-specific biomarkers of PD have been identified so far [13]. It is now actively being attempted to implement a closed-loop neuromodulation device for the PD treatment.

Rosin and colleagues conducted a feasibility test of closed-loop DBS on primate model of PD [45]. The purpose of this research was to show that closed-loop neuromodulation has better effect than conventional open-loop neuromodulation in terms of ameliorating symptoms of bradykinesia and akinesia. They showed this from accelerometer recording traces from limbs and SUA firing rate of the globus pallidus (GP). For the open-loop stimulation, they applied a continuous 130 Hz electrical stimulation. For the closed-loop stimulation, they conditionally applied 7 single pulses of same frequency when abnormal SUAs were detected in GPi or M1. Several signal processing techniques were used to analyze the effects of stimulation. A template subtraction method was used to remove stimulation artifacts [21, 22]. Spike detection/sorting was performed by a template matching algorithm [46]. Wavelet transform was applied to observe changes in oscillatory activity over time. As a result, they compared the firing rate and oscillatory activity of GPi before and after the stimulation, and found that the firing pattern of GPi can be

altered by both closed- and open-loop stimulation; however, closed-loop stimulation of 80 ms latency had the most significant positive effect. Accelerometer recording results also showed that closed-loop neuromodulation had a better effect on movement-related symptoms compared to open-loop neuromodulation.

Little and colleagues conducted blinded and un-blinded experiments using closed-loop DBS on eight human patients with advanced idiopathic PD with motor fluctuations and/or dyskinesia [47]. They tried to verify that closed-loop DBS provides better energy efficiency and better clinical treatment effect than conventional continuous DBS. Beta-band (13–30 Hz) power of LFP in subthalamic nucleus (STN) was used as a marker of PD symptoms. In open-loop conditions, they applied continuous electrical stimulation of 130 Hz regardless of the beta-band power of STN. For the closed-loop DBS, stimulation was applied only when the beta-band amplitude exceeded $3.9 \pm 3.8\%$ of the mean beta amplitude. They also tested another strategy, in which the electrical stimulation was randomly applied with a similar inter-stimuli interval as in the closed-loop condition, but regardless of the changes in the beta-band power of STN. To analyze the beta-band power of LFP, they used a bandpass filtered and rectified the LFP signal. The 3-stage common mode rejection amplifier introduced in [31] was used to remove stimulation artifacts generated by 130 Hz electrical stimulation. The result showed that motor scores were greatly improved in un-blinded and blinded conditions of closed-loop DBS. These results correspond to over 27% improvement compared to open-loop DBS. Moreover, in terms of energy efficiency, the closed-loop DBS was significantly better than open-loop DBS ($p < 0.001$).

Epilepsy

Epilepsy is a neurological disease characterized by spontaneous and recurrent epileptic seizures [48]. Transient electrical stimulation after predicting seizure onset enables an effective closed-loop neuromodulation for epilepsy patients [49]. Epileptic seizures recur unpredictably. However, the characteristics of neural signals during or before seizure can be utilized to predict seizure occurrence. A burst of energy is a prominent characteristic of preictal and ictal signals. Osorio and colleagues investigated the feasibility of using high-frequency (100–500 Hz) electrical stimulation when energy bursts are found before and during the occurrence of epileptic seizures [50]. The energy burst was characterized by a spectral power increase in 5–45 Hz band. For four of eight patients, the epileptogenic zone was directly stimulated (local closed-loop), and for the other four patients, the anterior thalami were stimulated (remote closed-loop). The algorithm used for epileptic seizure detection consisted of several steps. ECoG signals were filtered with a 5–45 Hz bandpass filter. And then, to discriminate the single or short bursts of interictal epileptic seizures from discharges from certain artifacts, an order-statistic, median filter was applied. The median filter was used instead of a moving average filter because the moving average filter is not robust to the outliers in the signal, and thus, was found to be better for seizure detection. Two sliding windows were used in this algorithm. The lengths of the two windows were 2 seconds and 30 minutes. The seizure events were detected if the ratio of the median values in the two windows exceeded the pre-defined threshold [51, 52]. As a result, the local closed-loop seizure rate was reduced 86% on average, and in the remote closed-loop condition, the seizure rate was reduced 40.8% on average.

Nonlinear features can be used for closed-loop neuromodulation for epilepsy. The RNS (Responsive Neurostimulation) system of Neuropace inc. aims to perform adjunctive therapy and is the only closed-loop neuromodulation system approved by the U.S. Food and Drug Administration (FDA) for commercial use. Many clinical reports have been published on the RNS [41, 53-57]. A pivotal study was conducted with the approval of the U.S. FDA, and the algorithms the system uses were described [53] . Human patients with medically intractable partial onset seizures from one or two foci ($n = 191$) were recruited. Randomized multicenter double-blinded task was conducted for the evaluation ($n = 97$ for treatment group, $n = 97$ for sham group). Three signal processing algorithms were used for detecting seizures, and they all used a sliding window and pre-defined threshold [56]. The first method is called line length. It measures the length of a signal in a given time interval. This method is a slightly transformed version of Katz's algorithm, which is used for measuring the fractal dimension [58]. Specifically, this method compares the mean line length of the signal in a long sliding window and short sliding window. If the ratio exceeds an absolute or relative threshold, it detects the events. Either positive or negative threshold values can be used because the negative threshold means a reduced line length. In this case, the detected event may indicate an electrodecremental event of the brain or decreased frequency. The second method is an area detection tool [59, 60]. Similar to the line length method, this method also uses sliding windows. It compares the area under the short-term window and long-term window to detect changes in signal energy. The third method is a bandpass detection tool or half-wave decomposition tool [61]. It segments the electrographic signal into half-waves using local minima and local maxima. This method counts the half-waves that exceed a pre-defined amplitude and duration in a given window. If the number of half-waves exceeds the pre-defined threshold, it detects the events. The seizure occurrence rate was significantly reduced in the treatment group (37.9%) compared

to the sham group (17.3%). Additionally, the number of people who had a 50% reduction in frequency was 44% after one year and 53% after two years. Therefore, treatment with closed-loop neuromodulation has a significant effect on reducing seizure occurrence.

Inter-regional phase synchronization also provides a good candidate for biomarker of epilepsy. One widely used method for measuring phase synchronization is phase locking value (PLV) [62]. Unlike traditional methods for synchrony such as spectral coherence, PLV measures only phase differences between two signals and determines how well the difference is locked over time or over trials. Abdelhalim and colleagues designed an ultra wideband 64 channel closed-loop DBS system-on-chip in which phase synchronization is used as a biomarker of epilepsy [43]. They conducted two experiments using LFP from freely moving epilepsy model rats, and human ECoG data from epilepsy patients. The LFP was analyzed to detect seizure events and it was found that phase synchronization at 8 Hz increased ~20 seconds before the seizure onset. Also from human ECoG, it was found that the magnitude and phase synchrony increased before and during seizure onset. It was also feasible to detect seizure event from both features, but the phase synchronization was better as an index of seizures which results in better for early detection.

Chronic pain

For the treatment of chronic pain, neuromodulation has long been investigated as an alternative to chemical methods or surgery since the first use of spinal cord stimulator [63]. However, few studies have been conducted on closed-loop neuromodulation for chronic pain. Posture-responsive spinal cord stimulation is the only closed-loop neuromodulation system that is applied clinically so far [64-66]. Most neuromodulation for the chronic pain is open-loop type. The stimulation parameters are adjusted based on behavior, from the pain intensity scale [67].

Zuo and colleagues recorded and analyzed neural signals from wide dynamic range (WDR) neurons in the dorsal horn of the spinal cord and discriminated noxious and innocuous stimuli from the firing rate of WDR neurons [68]. They used the firing rate of the WDR neurons to trigger electrical stimulation on the periaqueductal gray (PAG) to inhibit pain-related neural activities. When the firing rate of WDR neurons was higher than the predefined threshold, it was assumed that the given stimuli were noxious. Three types of stimuli were used in this experiment, including brush, pressure and pinch. The threshold was set to the arithmetic average of the firing rates from brush stimuli and pinch stimuli. Thereby the system predicted the pressure stimuli as marginally noxious and the pinch stimuli as noxious. Almost no stimulation was induced by brush stimuli, and significantly more stimulation was triggered by pressure and pinch stimuli. The electrical stimulation on the PAG could effectively reduce the firing of WDR neurons. It was concluded that the developed algorithm can discriminate innocuous and noxious stimuli based on neural activity.

CONCLUSION

The main purpose of closed-loop neuromodulation is to stably and effectively treat neurological disorders. Information on states of neural systems is crucial for effective and optimized stimulation, and an appropriate neural signal processing technique is required. This article provides an overview of the current status of neural signal processing techniques for closed-loop neuromodulation.

Stimulus-evoked neural activity from the signals recorded during electrical stimulation is required to ensure effectiveness of stimulation and minimize feedback delay. However, electrical stimulation induces distortion in neural activities. The interpolation method is widely used for stimulation artifact removal. This method shows less computational load with simple algorithms, whereas it causes the loss of neural activities during stimulation. The template subtraction method was developed to minimize the contamination of neural activity from stimulation artifacts. Because of the computational load, however, the template subtraction method may not be effective for implantable neuromodulation systems. Novel methods have been under development, especially for an implantable device with a computationally fast and effective algorithm. In addition to digital signal processing, dedicated hardware has been proposed for constructing cost-effective implantable closed-loop neuromodulation systems.

Neural signal-based biomarkers reflecting the patho-physiological statuses of patients are essential for closed-loop neuromodulation, and they should be developed from an understanding of the relationship between clinical states and neural signals. Disease-specific characteristics should be quantified from neural signals, possibly from firing pattern of SUA, neural synchrony and rhythm, and inter-regional functional connectivity. In epilepsy, suppression of seizure activity along with electrical stimulation can be provided by predicting seizure onset. Furthermore, adaptive stimulation in a specific brain area alleviated symptoms of other neurological disorders such as PD and chronic pain.

We expect that this article will serve as a valuable resource for further development of neural signal processing techniques for closed-loop neuromodulation. Advances in closed-loop neuromodulation in the future will benefit from efficient neural signal processing techniques based on an understanding of abnormal brain function associated with neurological disease.

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CONFLICT OF INTEREST STATEMENTS

Cha K declares that he has no conflict of interest in relation to the work in this article. Yeo D declares that he has no conflict of interest in relation to the work in this article. Kim K declares that he has no conflict of interest in relation to the work in this article.

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