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Neural function rebuilding on different bodies using microelectronic neural bridge technique

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Abstract: A microelectronic circuit is used to regenerate the neural signals between the proximal end and the distal end of an injured nerve. An experimental scheme is designed and carried out to verify the feasibility of the so-called microelectronic neural bridge (MNB). The sciatic signals of the source spinal toad which are evoked by chemical stimuli are used as source signals to stimulate the sciatic of the controlled spinal toad. The sciatic nerve signals of the source spinal toad, the regenerated sciatic signals in the controlled spinal toad, and the resulting electromyography (EMG) signals associated with the gastrocnemius muscle movements of the controlled spinal toad are displayed and recorded by an oscilloscope. By analyzing the coherence between the source sciatic nerve signals and the regenerated sciatic nerve signals and the coherence between the regenerated nerve signals and the EMG signals, it is proved that the regenerated sciatic nerve signals have a relationship with the source sciatic nerve signals and control shrinkage of the leg of the controlled toad.

Key words: neural function regeneration; electromy-ography (EMG); microelectronic neural bridge; coherence function

Injury on a central nervous system (CNS) in a biologic body, especially on a spinal cord, may result in a serious disability. When the spinal cord of a patient is injured, the body part below the injured segment may incur flaccid paralysis and loss of sensation since the injured spinal cord cannot transfer the motor commands from the brain down to the body part either partially or completely. As a result, spinal cord injured (SCI) patients would lose their mobility. This is not only extremely agonizing to the patients themselves, but also a heavy burden for their families and society. Therefore, it is of significance to study some techniques which enable the detection, transmission, and functional regeneration of neural signals for restoration of the lost functions of SCI patients.

Research efforts on the SCI have made great progress in recent years, and some new techniques and methods have been adopted to solve or relieve SCI caused disabilities. The method for cellular replacement is to fill lesions with tissue specific regeneration-competent cells that can replace or rescue the dying cells, or to activate endogenous neural progenitor cells which can biologically act similarly[1]. Intravenously injected neural progenitor cells (NPCs) can be used to migrate into the lesion site of a rat spinal cord and promote functional recovery[2]. Multipotent neural stem cells (NSCs) have the potential to differentiate into neuronal and glial cells and are therefore candidates for cell replacement therapy after CNS injury[2-3]. Also, implanted NSCs constitutively secrete significant quantities of several neurotrophic factors that support host axonal regeneration after SCI[4]. However, implantation of NSCs alone does not produce a significant restorative effect because the majority of the NSCs is engrafted into the spinal cord differentiated with an astrocytic phenotype[5]. Until now, relatively safe and efficient transplantation techniques have not yet been found.

Since 2004, we have conducted the study of the detection and regeneration of neural signals[6-7]. The proposed concept in this paper is the signal regeneration and function rebuilding of an injured spinal cord that are realized by using a microelectronic neural bridge (MNB). Using rats as the animal subjects, more than 20 experimental trials have already been carried out in our laboratory and a series of results have been obtained and published[8-11]. The previous results demonstrated that the functions of an injured spinal cord can be partially rebuilt when the spinal cord signals can be successfully regenerated. With these encouraging results, we hypothesize in the current paper that neural signals can be taken out from a spinal cord and directly transmitted to the controlled object by an electronic system, so that a part of the neural functions of the controlled biological body can be regenerated. In order to verify this hypothesis, a neural signal is obtained and applied at the input of the MNB system in our experiment, in which spinal toads are used instead of rats.

For the sake of avoiding the conduction of the organism itself, or the introduction of other interferences, we design an experiment for neural function regeneration by using sciatic nerve signals of separate spinal toads. The sciatic nerve signals of one toad are regenerated through the MNB system on the sciatic nerve of another toad. We observe and monitor the sciatic nerve signals of spinal toads before and after the signal regeneration and the resulting EMG signals associated with gastrocnemius muscle movements. Furthermore, we calculate the correlations and delay time between those signals. We can conclude from the numerical calculation results that neural signal regeneration and function rebuilding

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are possible.

The animal experiments including a microelectronic system, the electrodes, and others are further described in the next sections of this paper.

1 Microelectronic Neural Bridge System

The schematic of the microelectronic neural bridge system is shown in Fig. 1. It consists of electrodes, an input buffer, an instrument amplifier, a signal processing unit, a functional electrical stimulation (FES) driver, and nerve stimulating electrodes.

The electrodes that are in contact with the proximal nerve are used to detect the weak neural signals from the nerve (Note that it is the sciatic nerve of the source spinal toad in this paper). After amplification by a high-gain and low-noise amplifier, the neural signal is sent to the signal-processing unit, where a band pass filter is used. The signal is then applied to the FES driver. In the last stage, a high enough voltage/current is applied to the stimulating electrodes to evoke a neural signal in the distal nerve, i. e., the sciatic nerve of the controlled spinal toad. The neural function regeneration is achieved on the controlled toad muscle in the experimental demonstration.

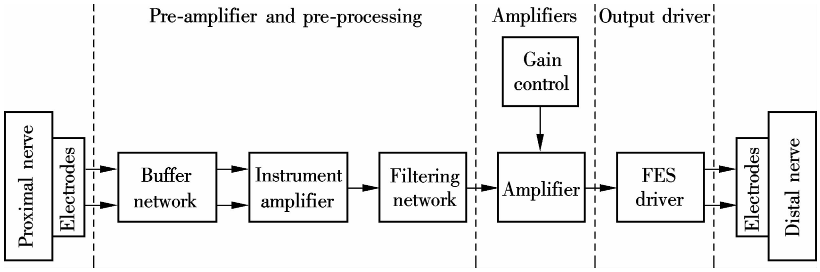

Fig. 1 Block diagram of microelectronic neural bridge system

In the experiment, two pairs of electrodes and one microelectronic module made of discrete devices or integrated circuits (IC) are used. The module made of discrete devices including commercial operational amplifiers is shown in Fig. 2.

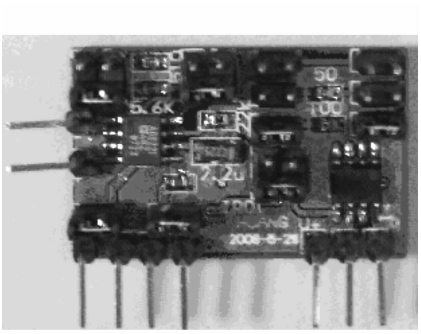

Fig. 2 Photograph of microelectronic neural bridge system made of discrete devices

The neural-bridging IC realized in a CMOS process consists of a low-noise pre-amplifier, a current-mode instrument amplifier, an output buffer and a biasing circuit with a constant trans-conductance. The 3-dB bandwidth of the system is from 10 to 2 000 Hz. The output current of the FES driver is adjustable from 0 to 7. 8 mA. The detailed description of the IC design is described in Ref. [12].

In the experiment, the neural signals are evoked in the nervous system of one toad by dripping a drop of 1% sulfuric acid on the toes of the left foot. As a result of conditioned reflex, the spinal toad withdraws its leg with the signal is applied. In order to ensure that the electrode is in good electric contact with the sciatic nerve of the toad, hook-type electrodes are used as both the detecting electrode and the FES electrode.

In order to study the relationship between the neural signals and the muscle locomotion, the EMG (electromyography) signals on the gastrocnemiuses of the two toads are also monitored during the detection of the sciatic nerve signals. Acupuncture needles are used as electrodes for EMG monitoring[13-16].

2 Animal Experiments

In this experiment, spinal toads are used. There are two advantages in using the spinal toads: 1) Since an anesthesia is not required for a toad, which is not a high-class vertebrate, the generation and transmission of neural signals are not inhibited and the generation of neural signals by an FES is not inhibited; 2) As amphibians, toads can maintain the biological activity for a long time without the control of the brain. Both of the advantages are helpful for the experiment of neural signal regeneration.

In our earlier experiments of neural signal regeneration, neural signals were induced by a square-wave electrical stimulation. In that situation, there always existed a stimulus artifact due to the conductive features of the organism itself[17]. In this experiment, we introduce a kind of chemical stimulation to induce nerve signals by applying a drop of 1% sulfuric acid on the longest toe of the source spinal toad. This can ensure that the recorded signal is a neural signal without the stimulus artifact.

The animal experiment system is shown in Fig. 3. Two spinal toads with their heads cut off are positioned and fixed on a board. The skin of the right side of the thigh is cleaved and the sciatic nerve is isolated with a threading standby. Three pairs of hooked electrodes are hitched onto the sciatic nerves. Two pairs of acupuncture needle electrodes are penetrated into the muscles of the left legs of two toads for EMG signal recording. In order to reduce artifacts, a metal coil is circled between the hook electrode and the needle electrode on the legs of the two toads and is grounded. The spinal toads have show reaction in the absence of any stimulus. Applying a drop of 1% sulfuric acid onto the toes of the left leg of the source spinal toad can cause the leg to withdraw due to conditioned reflex. After the sciatic nerve signal of the source spinal toad has been transmitted to the sciatic nerve of the controlled spinal toad through the microelectronic neural bridge system, we can observe that the left leg of the controlled spinal toad has a similar reaction to that of the source toad. The reaction and movement of the biological body through the neural signal derived from one toad, transmitting in the MNB, and then stimulating another toad is successfully demonstrated by conducting the toad experiment and recording by a video camera.

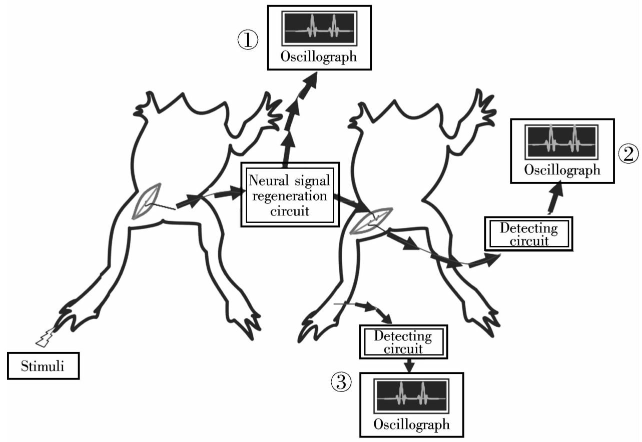

Fig. 3 Illustration of animal experiment for neural signal regeneration between two toads by MNB technique

The sciatic nerve signals of two spinal toads are digitally stored with the sampling rate of 2×10^4 points per second for off-line analysis. Fig. 4(a) shows a set of the recorded signals. The waveforms ① to ③ are the signals detected on the sciatic nerve of the source spinal toad, the signal detected on the sciatic nerve of the controlled spinal toad, and the EMG signal detected from the left leg of the controlled spinal toad, respectively. Fig. 4(b) shows the details of a part of the signal in Fig. 4(a), which will be discussed in next section.

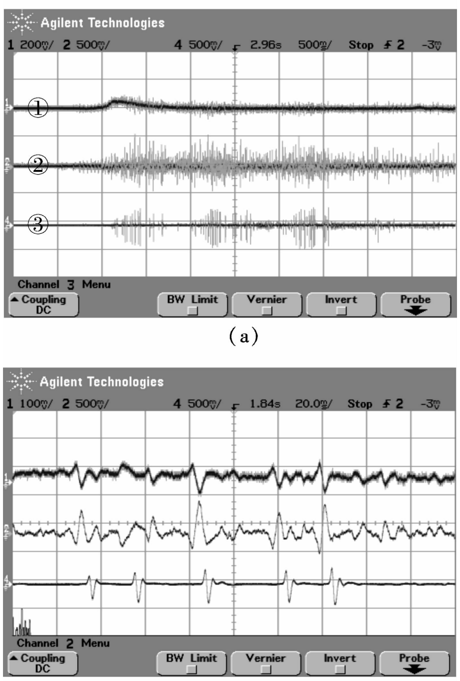

Fig. 4 Sciatic nerve signals and EMG signals observed in a neural signal regeneration experiment

3 Analysis of Experimental Results

The analysis of the functional coupling between the muscular activity and the simultaneously recorded oscillatory neural activity at different levels of the motor system has provided important insights into the neural control of movement[18]. The coherence function ρ_{xy} is widely used for estimating the similarity, synchronism, or functional coupling between two oscillatory signals[19], which can be defined as

$$\rho_{xy}^2 = \frac{\left(\sum_{n=-\infty}^{+\infty} x(n)\, y(n+m)\right)^2}{\sum_{n=-\infty}^{+\infty} x^2(n) \sum_{n=-\infty}^{+\infty} y^2(n)} \tag{1}$$

where $x(n)$ and $y(n)$ are two discrete signals; m is the number of shift points, and the delay time can be calculated by it. $m > 0$ means that sequence $y(n)$ shifts to the left; $m < 0$ means that sequence $y(n)$ shifts to the right. Different ρ_{xy} can be worked out for different m values.

The coherence function is a normalized correlation function, and it can measure the relative linearity and delay time between two signals. The value of the coherence has nothing to do with the magnitude of the oscillatory signals and it is convenient for comparing the degree of relativity. It can not only express the phase coherence, but also express the phase-shift (or delayed) coherence. The coherence value indicates the strength of the coupling in the time domain. It is mathematically bounded between -1 and 1, where 1 indicates a perfect linear relationship and 0 indicates no linear relationship.

In order to examine the similarity of the source sciatic nerve signal and the regenerated sciatic nerve signal on the controlled toad sciatic nerve and to analyze the functional coupling between the generated sciatic nerve signal and the muscular activity, the correlation analyses of the signals shown in Fig. 4(b) are performed and the results are shown in Fig. 5.

The results in Fig. 5(a) shows that the sciatic nerve signal of the controlled spinal toad is delayed for 0.2 ms in relation to the sciatic nerve signal of the source spinal toad. The cross-correlation function reaches the maximum value of 0.807 9. It means that the signal in the sciatic nerve of the source toad is successfully transmitted to the sciatic nerve of the controlled toad through the microelectronic neural bridge.

Fig. 4(b) shows the details of a segment in Fig. 4(a). Fig. 5(b) shows the rough relationship between the waveform ② of the sciatic nerve signal and the waveform ③ of the EMG signal of the second toad in Fig. 4(b). The EMG signal is delayed by 4.9 ms in relation to its regenerated sciatic signal and the cross-correlation coefficient is 0.525 7. It is proven that the EMG discharge is significantly related to the sciatic nerve signal. There is causality in the relationship between the reflex action and the sciatic signal.

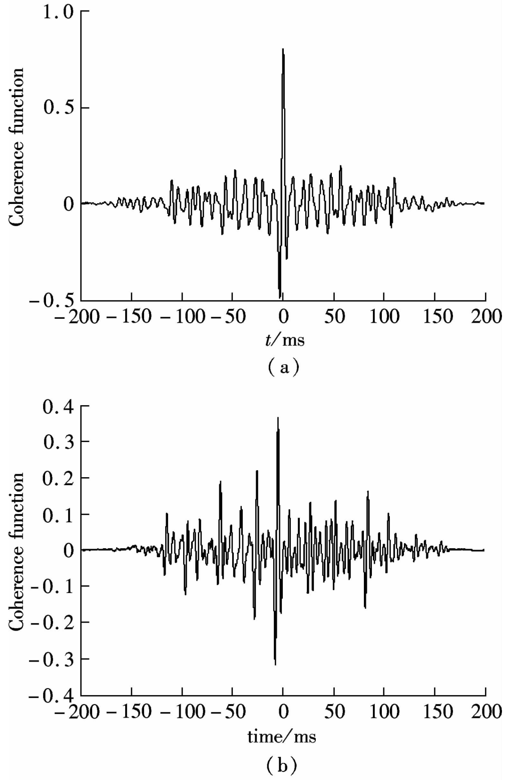

Fig. 5 Analysis of coherence function. (a) The coherence function between two spinal toads' sciatic nerve signals; (b) Coherence function between EMG signal and sciatic nerve signal of controlled toad

4 Conclusion

An experimental scheme is designed and conducted to verify the performance of the technique of the microelectronic neural bridge in regenerating neural signals. In this paper, it is described that the sciatic nerve signal derived from one toad is regenerated by another toad. The MNB technique demonstrates and proves to be feasible through a series of experiments. The neural signals and the EMG signals are recorded, and the good relationships between the nerve signals and the EMG signals are revealed. The results also show that there is a directional causality predominantly from sciatic signals to EMG signals corresponding to the significant coherence between sciatic signals and EMG signals. This work builds up a basis for further study on the relationship between the action and the neural signal.

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采用微电子神经桥实现的异体神经功能重建

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摘要:介绍了在损伤的远端神经与近端神经间利用微电子神经桥实现神经信道桥接的技术,设计并实施了一个实验方案,验证了微电子模块实现神经信道桥接的可行性. 以信源脊蟾蜍在化学刺激下诱发的坐骨神经信号作为信号源,激励受控脊蟾蜍的坐骨神经,控制其动作. 通过示波器观察并记录了信源脊蟾蜍坐骨神经信号、再生后的受控脊蟾蜍坐骨神经信号及其肌电信号. 通过分析信源脊蟾蜍坐骨神经信号与受控脊蟾蜍坐骨神经信号以及受控脊蟾蜍坐骨神经信号与肌电信号间的互相干函数,证明再生后的受控脊蟾蜍坐骨神经信号与信源脊蟾蜍坐骨神经信号有关,并对受控脊蟾蜍的缩腿动作起着控制作用.

关键词:神经功能重建;肌电信号;微电子神经桥;相干函数

中图分类号:Q426