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An implantable device for neuropsychiatric rehabilitation by chronic deep brain stimulation in freely moving rats

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Successful practice of clinical deep brain stimulation (DBS) calls for basic research on the mechanisms and explorations of new indications in animals. In the article, a new implantable, single-channel, low-power miniature device is proposed, which may transmit pulses chronically into the brain nucleus of freely moving rats. The DBS system consists of an implantable pulse generator (IPG), a bipolar electrode, and an external programmer. The IPG circuit module is assembled as a 20-mm diameter circular board and fixed on a rat's skull together with an electrode and battery. The rigid electrode may make its fabrication and implantation more easy. The external programmer is designed for bidirectional communication with the IPG by a telecontrol transceiver and adjusts stimulation parameters. A biological validation was performed in which the effects of electrical stimulation in brain nucleus accumbens were detected. The programmed parameters were accurate, implant steady, and power sufficient to allow stimulation for more than 3 months. The larger area of the electrode tip provided a moderate current or charge density and minimized the damage from electrochemistry and pyroelectricity. The rats implanted with the device showed a reduction in morphine-induced conditioned place preference after high-frequency stimulation. In conclusion, the DBS device is based on the criteria of simple technology, minimal invasion, low cost, small in size, lightweight, and wireless controlled. This shows that our DBS device is appropriate and can be used for preclinical studies, indicating its potential utility in the therapy and rehabilitation of neuropsychiatric disorders. *NeuroReport* **28:128–133 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

High-frequency deep brain stimulation (DBS) exerts a blocking effect on the stimulated brain region and produces clinical benefits [1]. In comparison with regional lesioning and thermocoagulation, DBS offers greater functional adaptability and safety because of its adjustability and reversibility [2]. Thus, DBS has been used to treat Parkinson's disease, dystonia, tremor, obsessive-compulsive disorder, Tourette syndrome, depression, dementia, epilepsy, obesity, and drug addiction [3–5]. Further application of DBS to modulate physiological disorders, such as blood pressure, respiration, and micturition, is also expected [6]. However, despite the numerous potential uses, the precise mechanisms of DBS and optimal neural targets remain largely unclear.

A clinical DBS device typically consists of an implantable pulse generator (IPG), an implantable multipolar DBS lead kit, and an external programmer [7,8]. The IPG contains a circuit module and battery. All these parts are hermetically sealed in a titanium case and connected with the lead through the adaptors, which are sealed in medical-grade epoxy. Aided by neuroimaging and stereotaxic surgery, the DBS electrode is implanted into a specific brain region and the external port of its linker extends to an anchoring site on the skull surface. The IPG is placed subcutaneously in the chest or other part of the body and connected with the linker of the DBS lead. This kind of DBS system has been successful in clinical practice. However, to explore mechanisms, optimize targets, or evaluate new indications, this DBS design is unsuitable for small laboratory animals (e.g. for rat). It is also difficult to ensure the reliability of the implanted device in long-term experiments. For these reasons, a few small DBS modules have been constructed for rats [9–11] and mice [12,13].

In the present study, an implantable single-channel DBS device was developed for a long-term experiment in rats. Its prototype, in our previous study, had been proved to be effective in reducing morphine reward in rats trained to show conditioned place preference (CPP) [14]. Compared with the reported devices, our design has

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distinctive features. Here, its detailed construction, parameters, fabrication, and its implantation into rats are described, including a new design to minimize the risk of tissue damage because of electrochemistry and pyroelectricity.

Methods

Architecture of the deep brain stimulation device

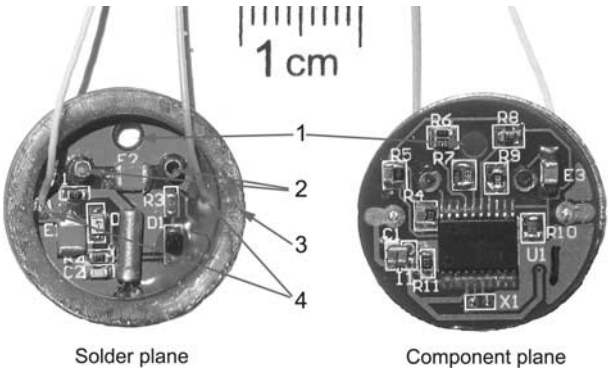
The DBS device is composed of an IPG, a stimulating electrode, and an external programmer. The system was designed on the basis of the criteria of simple technology, minimal invasion, low cost, and wireless operation. We designed the system prototype using commercial, off-the-shelf components except for the handmade electrode.

Implantable pulse generator

The pulse generator consists of a circuit module controlled by a microprocessor that is regulated with a telecontrol transceiver by an external programmer. The module, together with a telemetry coil, is assembled as a circular printed circuit board (Fig. 1). Its diameter is 20 mm and thickness is 4 mm. The circuit board contains a through hole (diameter 2 mm) and a pair of sockets for stimulation output, and the distance between the hole and sockets can be adjusted according to the brain site being targeted. The external end of the DBS lead is drawn through the hole and attached to the output sockets during the implantation procedure. The hole reduces the height of the entire implant. A CR2032 lithium battery (diameter 20 mm, thickness 3.2 mm, 3 V, 200 mAh) is used for power supply and is sufficient for 3 months of continuous operation. It is connected to the circuit module with flexible wires and sealed in medical-grade epoxy to ensure complete encapsulation before implantation.

Another feature is the approximately constant current output, rather than the commonly used constant voltage output. This constant current ($0.2 \sim 0.5$ mA) is realized by manual choice of a variable voltage according to the actual value of impedance in brain tissue read by the external programmer. The voltage regulation is realized by a variable resistor in series with the varying load. The constant current mode has the advantage of generating the same stimulation amplitude independent of changes in stimulating electrode resistance as the handmade electrodes varied with their impedances *in vivo*. With this design of the current source, the total component count and the total stimulator size are minimized, and the power waste in the pulse generator is decreased. In addition, the microprocessor can be remotely switched on and off and deliver information on the status of the IPG and its parameters to the external programmer by inductance coupling.

Fig. 1



The printed circuit board of the pulse generator with 1-through hole, 2-pulse output ports, 3-antenna coil, and 4-power supply ports. DBS, device's assembly and operation.

Trains of stimulus pulses are provided periodically (min per hour) at an interval time (alternate stimulus) to achieve electroneutrality (balance of positive and negative electron) and reduce electrochemical damage to brain tissue. The pulse frequency, pulse-width, and amplitude can be adjusted over a wide range. One of eight levels of voltage is chosen to maintain the value of established current according to the actual impedance. The formula is given by:

$$\begin{cases} I = \frac{V_1}{7-N+R} \ , & 0 \le N < 7 \\ I = \frac{V_2}{1+R} \ , & N = 7 \end{cases} , \qquad (1)$$

where I is current in mA, V_1 is 3 V, V_2 is 6 V, N is the voltage setting from 0 to 7, and R is the actual value of the impedance in kΩ. For example, if the impedance of an implanted electrode is 2.0 kΩ, the third level of voltage would produce a 0.5 mA current.

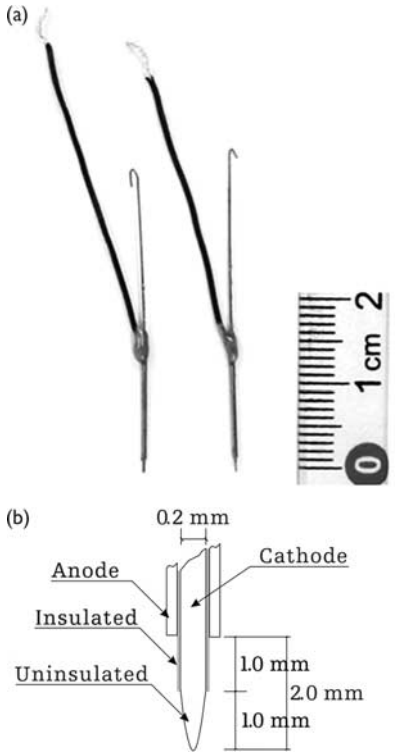
The firmware was written permanently into the memory of the microprocessor (i.e. all the instructions and code to program the stimulation parameters and shut down the device at low battery voltages). After being fabricated and tested, the circuit module and battery were coated with medical epoxy. Then, water-resistance testing began. The device was immersed in a physiological saline solution for two weeks and the leakage resistance was found to be higher than 200 MΩ.

There were six phases in the manufacturing process including fabrication of the circuit board, soldering of components, fabrication of the coil, circuit testing, encapsulation, and testing of the completed IPG instrument.

The deep brain stimulation electrode

The implantable DBS electrode consists of a bipolar concentric electrode and lead extension. The electrode was designed as a single-channel made of medical stainless steel ($Cr_1Ni_{18}Ti_9$) whose rigidity aided fabrication and implantation. Its outer metal tube (diameter 0.6 mm, length 15 mm) serves as a positive reference and

Fig. 2



The electrode structure with the appearance (a) and cutaway drawing of the electrode tip (b). DBS, device's assembly and operation.

the inner metal core (diameter 0.2 mm, length 35 ~ 40 mm) is the negative stimulating electrode. A medical epoxy layer is used for insulation between the inner cathode and the outer anode. The length of the rigid electrode is about 17.0 mm so that it extends 7–9 mm beyond the skull surface. One end of the electrode-lead wire was welded to the proximal end of the electrode, whereas the other was attached to the connector sleeve of the microstimulator during surgery (Fig. 2). The cathode–anode distance of the concentric electrode is short enough to generate a small range of electrical radiation. This feature, along with a moderate conductive area, avoids the occurrence of high charge or current density that may lead to tissue damage. To optimize the conductive area and impedance to decrease charge or current density for the electrode, the relationships among conductive length, area, and impedance of the electrode were tested *in vitro* and *in vivo*.

There were six phases in the fabrication processes including trimming of the steel tube and inner core, processing of the surface, lead welding, encapsulation and baking, and polishing of the electrode tip.

The external programmer

The external programmer is adapted from the portable programmer of an implantable cardiac pacemaker. The main components of the programmer are a microcontroller, a switching regulator, a receiver, and an LCD display. it is powered by a 9 V battery. The programmer is used for bidirectional communication with the implanted IPG through radiofrequency with an effective telemetry distance of 10 cm. It is capable of adjusting stimulation parameters, receiving electrophysiological information, and displaying operational status and electrode impedance from the IPG (Fig. 3).

Results

Deep brain stimulation device testing

Testing of the IPG verified that the device delivered stimulation pulses with user-defined frequency, pulsewidth, stimulus pattern, and current. In the present design, the output pulse was a monophasic, negative square wave (Fig. 5). Varying the pulse frequency did not affect the voltage output. After the IPG was immersed in a physiological saline solution for 2 weeks, the leakage resistance remained above 200 MΩ.

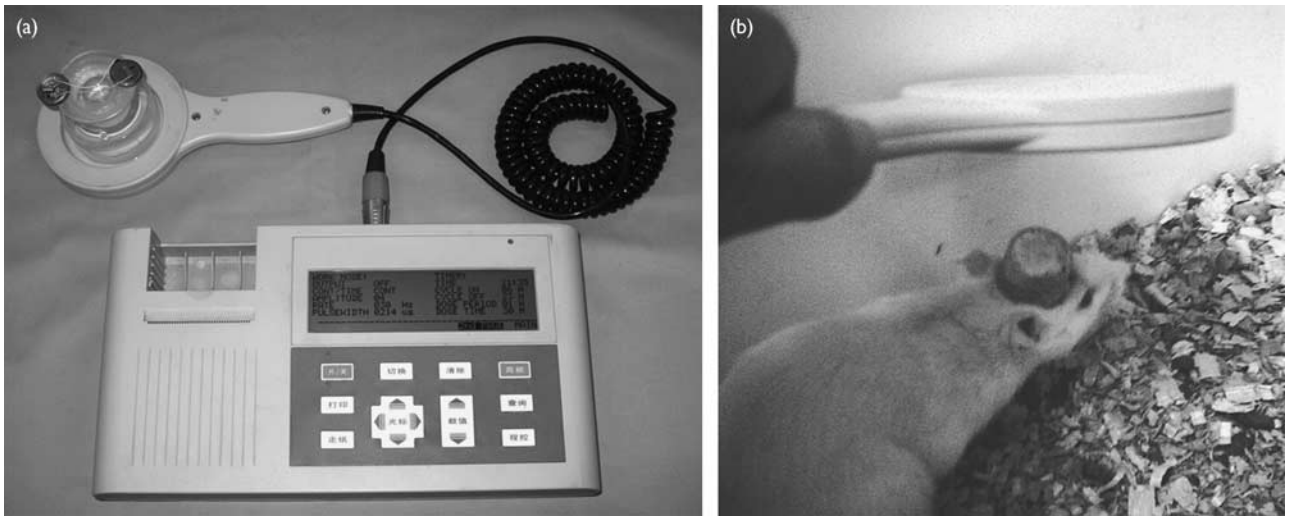
We found that 1.0-mm length and 0.5-mm^2 area are an appropriate geometry for the bare electrode tip. In this condition, the impedance of the electrode was 0.52 ± 0.06 kΩ in physiological saline and 2.10 ± 0.25 kΩ in brain tissue.

The external programmer displays the battery state (Ok or Low). The measured supply current was less than 1.0 μA at standby and less than 2.0 μA at no-load. Very little power was consumed during programming or telemetry. The leakage current of the direct current output was less than 0.1 μA. The parameters that can be set by the external programmer are shown in Table 1.

Implantation procedure

As a demonstration, the procedure of electrode implantation into the rat nucleus accumbens (NAc) is described. The NAc is currently the most promising target region for DBS treatment of drug addiction [15]. In the present experiment, rats were preanesthetized with diethyl ether, followed by full anesthesia with 2% sodium pentobarbital (50 mg/kg, intraperitoneal). Body temperature was controlled using a heating device. Three stainless-steel screws were placed into the exposed skull and a 2-mm diameter hole corresponding to the NAc was drilled into the skull until the cerebral dura mater appeared. The DBS electrode was stereotaxically implanted into the target, which was located in the core of the NAc. The coordinates for electrode implantation were as follows: AP + 1.8 mm, ML + 1.2 mm from the bregma, and DV − 6.5 mm from the dural surface. First, the end of the electrode was fixed firmly to the skull with screws using dental cement. After the cement was cured, the caudal end of the DBS lead was drawn through the hole and connected to the output sockets on the printed circuit board. Then, the circuit module, battery, and the end of the electrode were fixed to the rat's skull using cement

Fig. 3



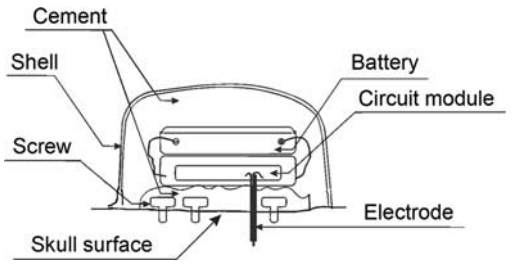
The external programmer and its working, which is powered by a 9 V battery (a). It is used for bidirectional communication with the implanted IPG through radiofrequency at an effective telemetry distance of 10 cm to adjust stimulation parameters, etc. The DBS device is being programmed with a telecontrol transceiver (b). DBS, deep brain stimulation; IPG, implantable pulse generator. DBS, device's assembly and operation.

Table 1 Parameter adjustment and measurement by the external programmer

Parameters	Range	Step width
Pulse rate (Hz)	1–200	1
Pulse width (ms)	0.03–1.40	0.03
Pulse strength (grade)[a]	1–7	1
Stimulator turn-on time (h)	0–24	1
Stimulator turn-off time (h)	0–24	1
Working on time (h)	0–24	1
Working off time (h)	0–24	1
Dose cycle (h)	0–24	1
Dose time (min)	0–60	1
Impedance measurement (Ω)	200–7000	100

[a]Strength is adjusted by change of the series resistance in the output circuit.

Fig. 4



Assembly and cutaway drawing of the implantable pulse generator device. DBS, device's assembly and operation.

and screws. Finally, the entire implant was covered with dental base acrylic resin powder to prevent the cement from detaching and a plastic shell was placed over the implant to prevent the rat from scratching it. The entire implant was less than 15-mm high (Fig. 4 [14]).

In general, rats could raise their heads, walk, and eat 2–12 h after surgery. Now and then, muscular rigidity made walking difficult, but the rats recovered fully 2 days later with good hygiene (grooming behavior). The rats had no difficulty raising their heads and no implants were broken off during the course of the experiments.

The overall dimensions of the device were 20 mm diameter and less than 8 mm thickness, including the circuit and battery. The weight of the circuit and battery together was less than 6.0 g. After connection encapsulation and implantation, the whole was 14–16 g, including the lead, dental cement, screws, and a plastic shell. The entire implant was a single package small enough to be safely implanted in rats. Animal care was in accordance with the guidelines approved by the National Institutes of Health Guide for the Care and Use of Laboratory Animals in the USA.

Biological validation of the deep brain stimulation device

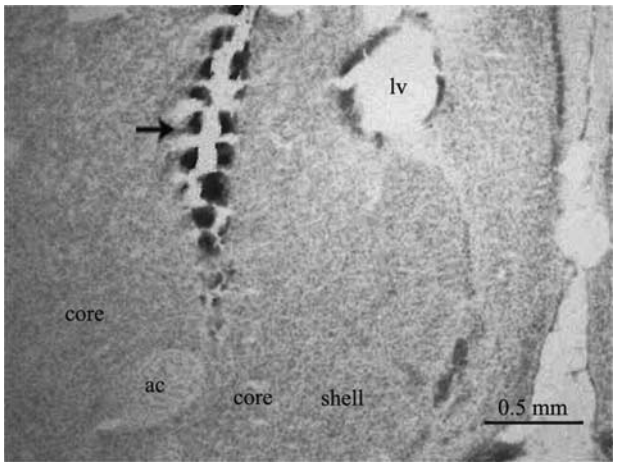
The prototype of our DBS device was previously shown to inhibit the reward properties of morphine in rats [14]. In the study, 7 days of injection of morphine at an increasing dose yielded an animal model by the test of CPP. The time that rats spent in the drug-paired side during the 900-s paradigm was recorded to assess individual preference. When rats spent much more time in the white than in the black compartment, it was considered that the phenomenon of morphine-seeking occurred. Then, the electrical stimulation was given as follows: 15-min On, 45-min Off, 15-min On, 45-min Off, and 15-min On on each day. The DBS parameters

consisted of a train of monophasic 0.21-ms square pulses at a frequency of 130 Hz and current strength was varied from 0.2 to 0.5 mA [16], which was similar to the clinical usage of DBS. Under a training protocol to acquire morphine-induced CPP, the rats that received DBS showed a reduced CPP score [14].

After completion of the experiment, a pathomorphological examination was carried out. Rats were anesthetized with pentobarbital (50 mg/kg, intraperitoneal) and administered a 100-mA current for 10 s. Then, the rats were perfused through the left cardiac ventricle with 150 ml solution of 10% formaldehyde and 2% ferrous potassium cyanide, followed by 150 ml physiological saline solution. The DBS device including the electrode was removed from the skull and the brain was dissected out. Coronal sections (100 μm in thickness) adjacent to the electrode were obtained using a cryostat (Jinhua YIDI Medical Appliance Co., Ltd. Jinhua, Zhejiang Province, China). After the sections were stained by Cresyl violet, the trajectory of the electrode was visible as a pucecolored track because of the pyroelectric injury (Fig. 5).

From the results, we found that the implanted electrodes were in the correct position. All animals were subjected to an examination of the trajectory of the electrode. The data from any animals with a wrong location of the electrode were deleted. No edema, cicatrix, gliocyte proliferation, and other abnormal condition were found in the area, and a further cellular investigation was not carried out. We found that the above was consistent with other reports [11]. All our procedures of animal experiments were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (USA) and approved by the Committee of Animal Use and Protection of North University of China.

Fig. 5



Electrode track. Photomicrograph showing that the end of the electrode track (arrow) is at the core of the NAc. ac, anterior commissure; core, represents the core part of the NAc, shell the shell part of the NAc; lv, lateral ventricle; NAc, nucleus accumbens. There was no significant tissue damage around the electrode's shaft and tip.

Discussion

This study introduces a new DBS device and its implantation method for rats. The device is relatively small and light, and radiofrequency bidirectional communication is used between the IPG and the controller to avoid the use of an externalized stimulator. Thus, our device is compatible for use in freely moving rats. The device can be applied easily in behavioral experiments, for example, those involving drug self-administration.

Appropriate for short-term use in animals – but not in humans – medical stainless steel was selected for the electrode rather than a platinum–iridium alloy. Another major reason for this selection was that its rigidity and low cost made it easy to fabricate and implant. For instance, platinum and platinum/iridium are not easy to solder, requiring spot-welding between the electrode and the other components. To balance the current or charge density around the electrode and decrease the damage from electrochemistry and pyroelectricity, three specific properties were realized: (i) a large effective conductive area (0.5 mm^2) of the end of the electrode, larger than the areas of 0.118 [9], 0.12, and 0.177 mm^2 [17,18] used in previous studies, (ii) the electrode impedance (2.4 kΩ) was smaller than 10 kΩ [9,11,19], and (iii) an intermittent pulse was used for electroneutrality. Meanwhile, hermetic encapsulation of the IPG, electrode, and battery ensured sufficient mechanical stability and durability. The capacity of the battery ensured that the device would function for 3 months. Its method of implantation, connection, and fixation allowed, in one case, an effective duration of more than 10 months. However, the present device could still be improved with respect to size, weight, and telemetry distance.

The previous results showed an inhibitive effect of DBS on morphine-induced reinforcement in rats and validated the device's reliability and implantation procedure [14]. Recently, DBS has been explored as a possible treatment for drug addiction. Among the NAc, subthalamic nucleus, dorsal striatum, lateral habenula, medial prefrontal cortex, and hypothalamus, preclinical DBS studies suggest the NAc as the most promising stimulation target for addiction treatment [5,15]. The success in preclinical studies and the expanding use of DBS in the treatment of other psychiatric disorders have led to clinical investigations dealing with addiction. A few case reports that the new technique of DBS has been used successfully to opioid-addicted patients [20–22]. The door has been opened, but the development of a suitable DBS therapeutic strategy for drug addiction remains challenging. Animal studies using small DBS devices will contribute considerably toward overcoming the existing problems.

Fortunately, more attention has been paid to the design of small DBS devices for animal use. Several versions have been published recently [9–13]. These devices are characterized by magnetic field-control [13], DBS and neural recording combinations [10], and replaceable battery and recyclable IGP [9], and some are light enough for use with mice in behavioral experiments [12]. Small DBS devices are an exciting research tool for neuroscience that enable the consideration of novel mechanisms and new indications for DBS, especially in the field of intractable neuropsychiatric/neuropsychological disorders.

Conclusion

This article describes a fully implantable, wireless, low-cost, single-channel stimulation device that can be fabricated in a laboratory. The stimulator generates charge-balanced monophasic current pulses into neural tissue in free-moving laboratory animals. Its function, stability, and dimensions are suitable for chronic DBS in rats and the implantation procedure is a minimally invasive surgery and well tolerated by the animals. The biocompatibility of the stimulation system is also validated by minimal tissue reaction around the electrode core and it is shown that chronic stimulation of the rat NAc reduces morphine addiction.

As an experimental means, the device may transmit various impulses into neural nuclei, and affect brain function and behavior. Therefore, it can be utilized in further exploration of mechanisms, treatment, and rehabilitation for neuropsychiatric and neuropsychological disorders.

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Conflicts of interest

There are no conflicts of interest.

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