

ZigBee-based Wireless Neuro-Stimulator for Improving Stroke Recovery

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ABSTRACT

Stroke is a leading cause of adult disability and the second-leading cause of death in Korea. It is also the third-leading cause of death in the United States, leading to a serious demand for new interventions to improve the quality of life in stroke survivors. To this end, direct cortical stimulation using an epidural electrode has been reported with promising results in animal and human studies, showing the potential for enhancing the recovery in chronic stroke patients. For optimal results, doctors must be able to modify the stimulation pattern as frequently as needed over a period of time for a given patient. However, severe aftereffects caused by stroke limit patients' activities, making regular doctor visits for treatment difficult. This study aims to develop a prototype of a telemedicine system to enhance stroke recovery by using a ZigBee-based wireless neuro-stimulator. The ZigBee is a stable platform for many low-power wireless applications. To allow stroke patients to remotely obtain neuro-stimulation treatments from their doctors, we connected the ZigBee to the internet. The system also allows doctors to personalize treatment based on the history of the stimulation parameters. The system developed here can also be beneficial as a common platform for a wide range of brain diseases and clinical care for which electric stimulation is used.

Key words: electrical brain stimulation, stroke recovery, rehabilitation, ZigBee, neural stimulation

INTRODUCTION

Stroke is a leading cause of adult disability and the second-leading cause of death in Korea. It is also the third-leading cause of death in the United States. Approximately two-thirds of individuals suffering a stroke survive and require rehabilitation

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(Hendricks et al., 2002; Kim et al., 2006a). The natural plasticity of the human brain generally allows some nervous system recovery between 3 and 6 months after the stroke, and stroke patients usually expect progressive recovery during that time. Medication and physical therapy are common treatments for strokes to facilitate nerve recovery (Beck et al., 2000; Neville et al., 2000; Kim et al., 2006b). While early rehabilitation treatment does help patients regain pre-stroke functions, recovery slowly subsides after the first month following the stroke and tends to level off and stagnate in the long term (Bonita and Beaglehole, 1988; Duncan, 1992; Brown et al., 2003; Calautti and Baron, 2003; Brown, 2006; Canavero, 2006). After about six months, stroke survivors benefit little from rehabilitative training and are left impaired (Duncan, 2000). Long-term interventional strategies to improve the quality of life in stroke survivors are therefore in great demand.

Recent studies have shown that electrical currents delivered to the cortex through transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) cause cortical stimulation that can modulate the cortical excitability of the human brain noninvasively (Calautti and Baron, 2003; Canavero, 2006). These techniques can also be used as therapeutic interventions to enhance recovery in patients suffering from the long-term aftereffects of stroke (Uy, 2003; Khedr et al., 2005; Kim et al., 2006c). It has been suggested that direct cortical stimulation through an epidural electrode may produce similar effects, possibly with more advantages (Kim et al., 2006c). To test this hypothesis, extradural cortical stimulation (ECS) to enhance recovery has been studied and has shown promising results in animal and human studies for enhancing recovery in chronic stroke patients (Brown et al., 2003; Brown et al., 2006; Canavero et al., 2006; Moon et al., 2007; Huang et al., 2008; Kim et al., 2008; Levy et al., 2008). The underlying process of the recovery improvements has not been fully understood. Possible explanations include improved neural plasticity due to the increase in neural activity with electrical stimulation as well as the reduction in the death rate of normal tissues around the lesion during the inflammatory period.

The application of direct electric stimulation for

stroke recovery is in an early stage, in contrast to the abundant research and clinical studies on commercial deep brain stimulators (DBS) for Parkinson's disease and epilepsy (Agnew et al., 1990; Luders, 2004; Theodore and Fisher, 2004; Weaver et al., 2006). To directly stimulate the cortical region, stimulating electrodes are implanted in the brain and an electric stimulator which is wired to the electrodes is shielded under the skin, requiring a wireless link for convenient operation of the implanted pulse generator (IPG). The commercial DBS systems provide magnetic and proximity RF links for the doctors to configure the IPG and control its operation. The spatial range of control, however, is limited to the extent that a dedicated controller device has to closely approach the patient's skin to access the IPG in clinical application.

Moreover, electrical stimulation therapy for stroke implies not just temporary diminishment of symptoms but also gradual recovery of the impaired functions. Ongoing modification of the stimulation pattern is essential during treatment. The stroke patients need intensive administration by doctors for optimal recovery. However, severe stroke after-effects often limit patients' activities, making regular doctor visits for treatment difficult.

The stimulator proposed in this study adopts a widely known low-power wireless communication standard ZigBee in order to extend the control range of IPG in space, reaching as far as remote hospitals or clinics through the internet. The proposed stimulator also provides for bidirectional communication, enabling continuous monitoring of nerve tissue and its surroundings, and consequently allows traditional rehabilitation methods to be augmented by neuro-modulation therapy. In this study, we aim to develop a prototype miniaturized electric stimulator for stroke recovery and a wireless communication pathway for extended and flexible use of the IPG.

MATERIALS AND METHODS

Preliminary animal experiment

The effect of electric stimulation was studied on focal brain ischemic model in the rat. Photothrombotic lesion were made in 20 rats on their

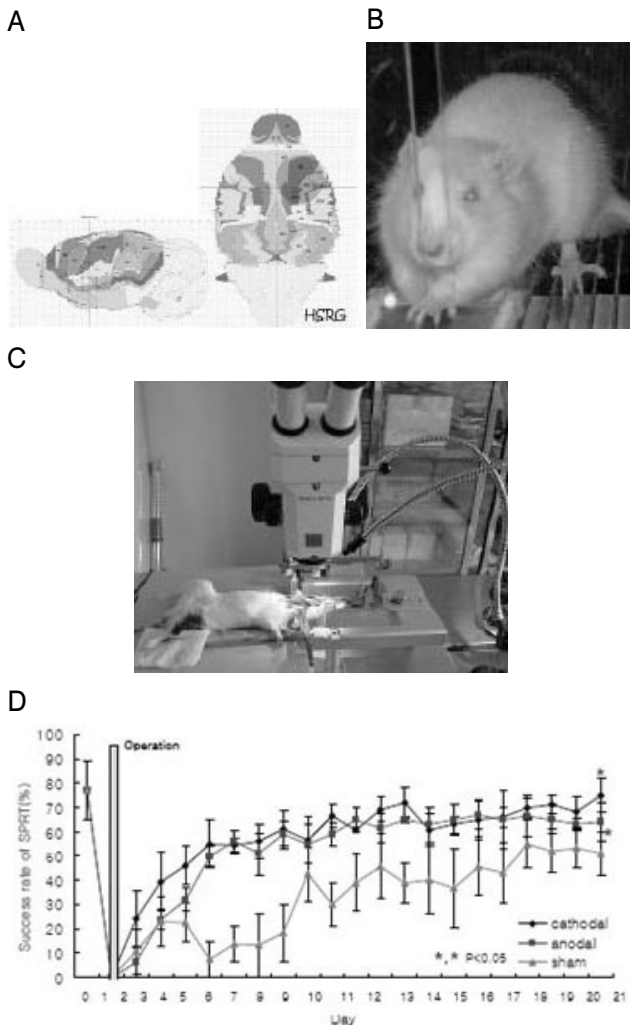


Fig. 1. Preliminary animal experiment to verify the effect of cortical electric stimulation. (A) The brain map of a rat. (B) Single pellet reaching task (SPRT) method to evaluate motor ability. (C) Stroke model by photo-thrombotic infarction. (D) Recovery rate of 3 groups of stroke induced rat SHAM, ANODAL stimulation, CATHODAL stimulation group.

primary motor cortex (M1) which is responsible for handling hand (forearm) movement as shown in Fig. 1A, C. Photothrombotic infarction was induced in the cortex opposite the preferred paw. Rats were anesthetized with a mixture of ketamine hydrochloride (100 mg/kg) and xylazine (10 mg/kg), heads fixed in a small animal stereotaxic frame and a skin incision was made in the frontoparietal area. A fiber optic cold illumination light source with 3 mm aperture (Fiberoptic Korea Co., Cheonan, Korea) was stereotaxically positioned 1 mm anterior to bregma and 3 mm lateral to midline on the skull, covering the area representing forelimb motor and part of sensory cortex. Cold light was irradiated on

the skull for 2 min, and a photosensitive dye Rose Bengal (20 mg/kg) was injected through a femoral vein, followed by additional illumination for 18 min. Then, a stimulating electrode was implanted immediately after induction of cortical lesions in all rats. A small (~3 mm circular) craniotomy was made at the anterior border of the illumination area to expose the peri-infarct cortex. A 3 mm diameter circular stimulating electrode (Oscor, Tampa, Florida, USA) was placed on the exposed dura and a reference screw on posterior parietal bone. The rats were divided in 3 different subject groups, which are, sham group (w/electrodes and w/o electric stimulation, n=10), anodal electric stimulation group (n=5) and cathodal electric stimulation group (n=5). Stimulation amplitude was set to half the movement threshold for individual animals, while 50 Hz frequency and 194 ms pulse duration were uniformly used. To measure the rate of motor function recovery, the kinetic ability of the rats are evaluated quantitatively using single pellet reaching task (SPRT) as shown in Fig. 1B before and after stroke. Success rate in SPRT is measured by the percentage rate of perfectly eating pieces as in Eq. (1).

$$\text{Success rate of SPRT} = \frac{\text{perfectly eating units}}{\text{all units ate}} \times 100 \quad (1)$$

Fig. 1D shows the measured daily success rates of the 3 groups during 3 weeks after the focal lesion was induced. The results show that the cathodal stimulation group recovered their motor ability up to 80% of their normal values after treatment. ANOVA showed that there is significant difference between the sham group and the stimulation groups ($p < 0.05$). Therefore, the electrical stimulation is thought to help the brain to recover motor function after stroke. Further researches to find better stimulation methods are ongoing.

IPG model and ZigBee communication system

Two types of pulses were used (anodal and cathodal) in the stimulation of brain tissue in the preliminary animal experiments (Kim et al., 2008). Chronic electrical stimulation of nerve tissue with only a monopolar pulse might damage some tissues and corrode the interfacing electrode. Such

corrosion significantly distorts the stimulation waveform (Theodore and Fisher, 2004) which makes it difficult to deliver the intended electric voltages or currents to the neural tissues concerned. The developed IPG model is capable of bi-phasic pulse generation. A bipolar or biphasic pulse can reduce cell damage and electrode corrosion. The bipolar pulse consists of pairs of main phase and compensating phase with opposite polarities for charge balance. It can furthermore selectively stimulate a cell body or axon under certain conditions if necessary (Theodore and Fisher, 2004). The H-bridge circuit can generate 3 different polarities with a single power supply. The amplitude of stimulation is adjustable with a D/A converter, DAC7617 (TI, USA). The IPG model includes the H-bridge, D/A converter, and microcontroller unit Atmega128L (Atmel, USA) for accurate generation and adjustment of stimulation waveforms. The Atmega128L is an 8-bit microcontroller with RISCH architecture and low power consumption characteristics. Fig. 2A shows the developed stimulation circuit. The IPG model has dimensions of $50 \times 37 \times 8$ mm³ and a weight of 7.4 g.

It should be noted that the animal experiments found no remarkable increase in recovery ratio after about 1 month of direct cortical electric stimulation treatment. For humans, it is expected that the implanted system should operate for about 6 months to cover the period in which functional recovery is most active.

The ZigBee link enables bi-directional communication between the neural stimulator and controlling equipment on outside. ZigBee is a standard small, low power radio-frequency communication protocol based on the IEEE 802.15.4 standard, designed for use in wireless personal area networking (WPAN) applications (Jung and Jeon, 2004). The low power characteristic is essential to the electrical system implanted in the body because battery replacement requires an additional surgical operation. Moreover, most of the electric power should be used for neural stimulation, while power consumption in the other parts of the system, including communication, should be minimized. A small ZigBee transceiver module was developed based on the design reference given with a commercial CC2420 ZigBee Development Kit (Chipcon, Norway). The CC2420 is

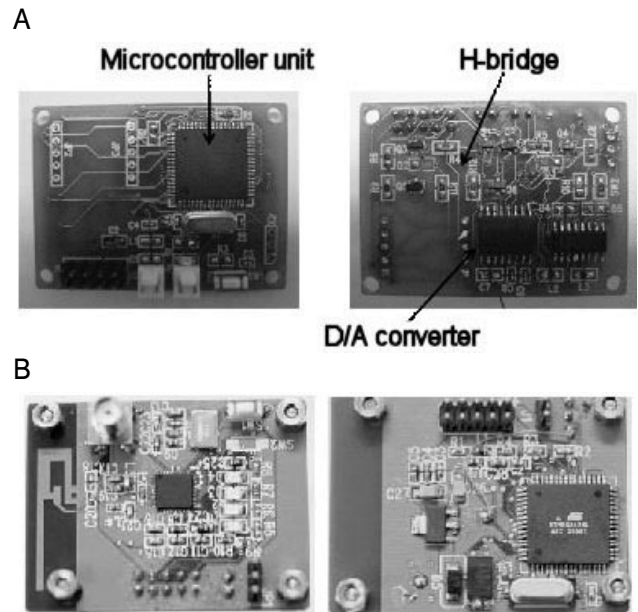


Fig. 2. (A) The miniaturized electrical neuro-stimulator circuit board composed of a microcontroller unit, H-bridge and D/A converter. Size of 50×37 mm² and weighing 7.4 g. (B) The ZigBee communication module. Size of $45 \times 40 \times 12$ mm³ and weighing 12.7 g.

an RF communication chip which supports the 2.4GHz IEEE 802.15.4 standard protocol. The RF chip was integrated with the Atmega128L microcontroller unit on a discrete IC level. A software protocol stack was embedded in the microcontroller unit to support ZigBee. Fig. 2B shows the transceiver module. The developed circuit board has physical dimension of $45 \times 40 \times 12$ mm³, which is the size of a small matchbox, and its weight is 12.7 g.

In addition to enabling wireless control, the ZigBee can connect the neuro-modulation system to a widespread communication network such as the internet or a mobile network. This network-based neuro-modulation system can provide a remote or tele-rehabilitation program exemplified by Fig. 3A.

The ZigBee is also capable of handling a large number of wireless connections within small range of area at the same time. Therefore, a ZigBee-based wireless rehabilitation program could manage many patients simultaneously in a local area. A relatively small number of doctors or certified personnel in a local rehabilitation center could therefore manage many stroke patients at a time, even during their training activities.

The IPG model was combined with the trans-

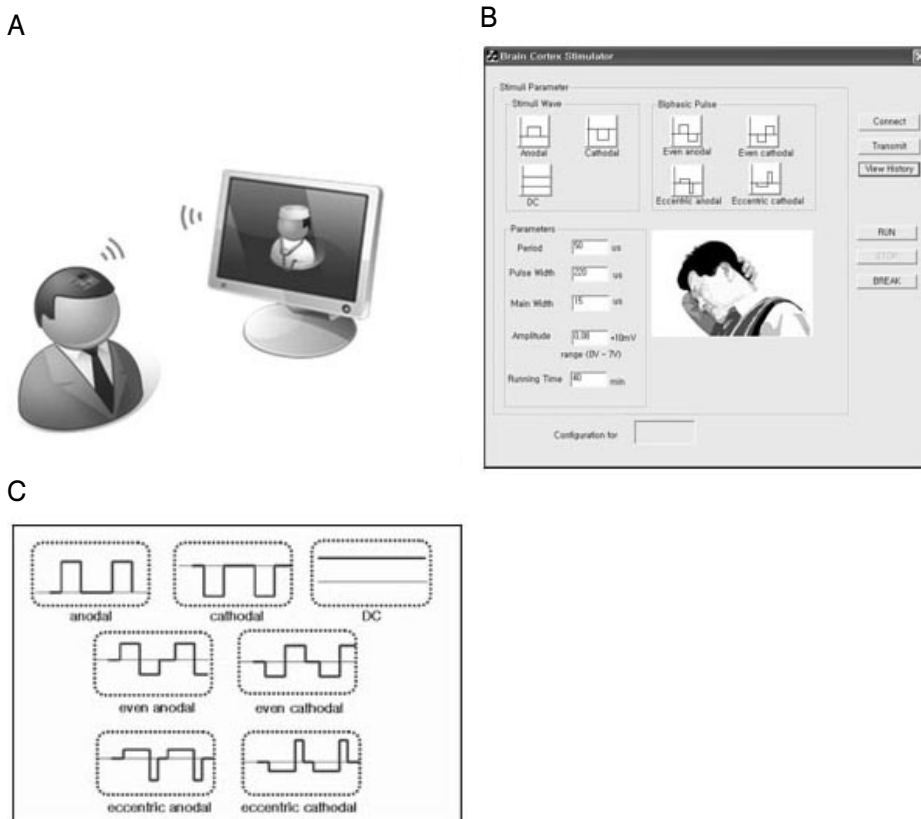


Fig. 3. A remote rehabilitation service for stroke recovery using a ZigBee-based neuro-modulation system. (A) The patient's IPG is connected to doctors at a remote site through the internet and PC. (B) GUI for configuring the electrical stimulator. (C) Various configurations of stimulation.

ceiver module to examine the possibility of future implantation, especially considering its size with all the functionalities of the wireless neuro-stimulation device enclosed in one small device.

Remote and wireless configuration of neuro-stimulator

The brain stimulation parameters can be configured by doctors from a remote site. The developed telemedicine system consists of the wireless IPG model linked to the TCP/IP via the ZigBee link mounted at a PC. The neuro-stimulator can be configured by selecting its ID and several parameters in a graphical user interface (GUI) software shown in Fig. 3B.

The neuro-stimulator configuration window provides the selection of such stimulation parameters as period, pulse width, amplitude and overall running time. The stimulation waveform can have different polarities and modes. Monopolar, bipolar and DC modes are as shown in Fig. 3C. Bipolar stimulation can be either even or eccentric. Both consist of charge balanced pulse pairs as mentioned above. The period and the pulse width are in

the range of several or tens of microseconds. The amplitude has values of several millivolts. The overall running time is usually about an hour per one day in regular operation. Since there are no commercial standards for neuro-stimulators for stroke, the ranges of parameters appropriate for neural tissue stimulation were selected based on those used in the preliminary animal experiments or based on a clinically available DBS Soletra Model 7426 (Medtronic) used for treating other movement disorder like Parkinson's disease and essential tremor.

The configuration parameters are loaded in a data packet for efficient and accurate wireless transmission over the air between the PC and the neuro-stimulator. The IPG model then correctly repeats the configured stimulation waveforms.

Chronic data management for optimal stimulation therapy

The periodic electrical stimulation treatment given by the proposed system would be also monitored continuously by the remote doctors. A record of the stimulation and the gradual recovery process is a

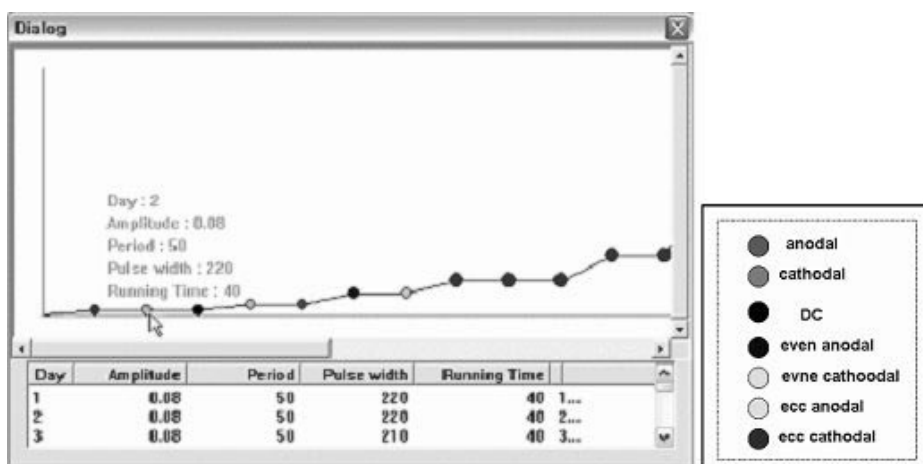


Fig. 4. Graphical visualization of the stimulation parameters. Each color indicates the polarity of stimulation in the amplitude-based display of chronic data.

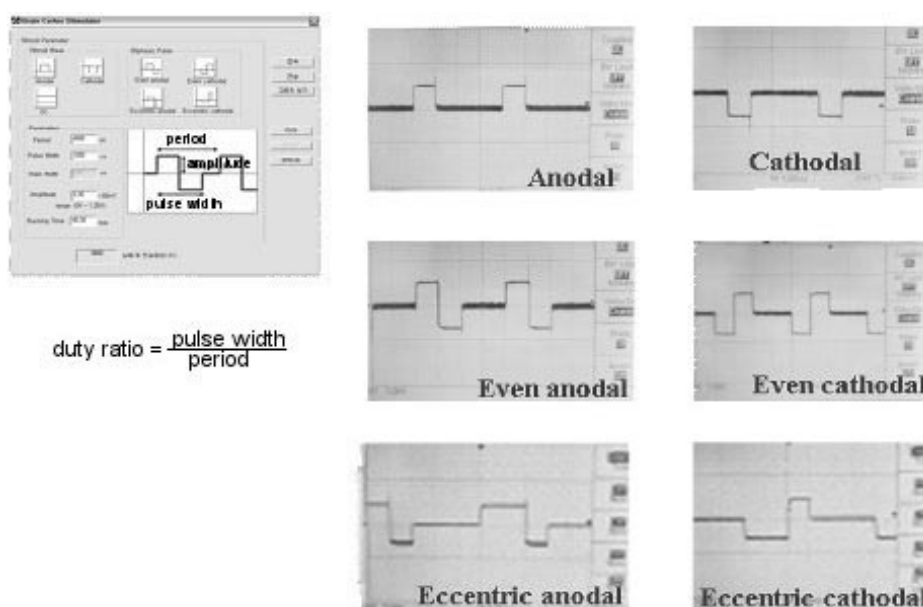


Fig. 5. Wireless configuration of the stimulator and its output waveforms measured by oscilloscope.

valuable resource in this type of neuro-stimulation therapy. The collection of data includes background information specific to the patient and the disease such as the times of attack, operation, and implantation of the neuro-electrodes and stimulator. The main objective of the system is to produce an easily visualized history of each patient's treatment containing quantitative data stored in a database as illustrated in Fig. 4. Clinical neurosurgeons can make use of this tool to gain insight into effective treatment programs. Doctors can correlate the history of the changes in stimulation parameters with the gradual recovery process of the patient.

Stimulation parameters are organized in the GUI according to their significance and effects. Since it is generally accepted that the amplitude of the

pulse has the strongest impact on the brain, amplitude is marked on the vertical axis. Each circle indicates one dose given by the doctor. The radius of the circle corresponds to the duration of each dose. The color shows the polarity and mode of stimulation; red is for anodal stimulation, green for cathodal, black for DC, blue for even anodal, light blue for even cathodal, yellow for eccentric anodal, and purple for eccentric cathodal. Additional details are shown when the mouse cursor moves over the circle.

RESULTS AND DISCUSSION

The prototype neuro-stimulator developed in this work is configured remotely through ZigBee and the

internet to generate the selected waveforms exactly, including DC, monopolar and bipolar pulses, as shown in Fig. 5. The wireless configuration worked reliably within a radius of about 10 m.

The connection to each patient was made using a direct database link and the ongoing information about stimulation was stored in the corresponding database.

For an extended use of a neuro-stimulator implanted in the body, most of the battery power should be concentrated on electrical stimulation of neural tissues rather than on communication. We therefore decided to transmit only the shape parameters of the waveforms instead of all the data points of the waveform. Another drawback to transmitting all the data points is that this requires a long communication time via RF transmission. A complete set of points would allow us to generate arbitrary waveforms; however, there is some potential risk in using high frequency RF transmission through the skin. The parametric transmission needs only about 10 bytes while the entire data point transmission requires about 400 bytes. The proposed method achieved both reduced power consumption and minimal RF exposure time. Table 1(a) shows the current consumption of the device under various stimulation configurations. The definition of the duty ratio is shown in Fig. 5. Table 1(b) shows the performance of our neuro-stimulator prototype compared with the technical specification of the Soletra Model 7426. Although the two systems have different working principles for different diseases and thus cannot be directly compared, Table 1(b) shows that our proposed system has better device performance, which might be useful for more precise experiments. The minimum pulse width (time resolution) is $1 \mu\text{s}$, the maximum repetition rate was 500 kHz, and stimulation voltage ranges from -3.3 to $+3.3$ V. The output voltage necessary for cortical stimulation for stroke recovery is much lower than 3.3 V (Moon et al, 2007). Cortical stimulation in animals, which will likely be the first application of the developed system, requires low voltages. Our device meets the requirements for a prototype and animal experiments.

The chronic data management capability of the remote stimulation system will help doctors understand what conditions improve recovery for a

Table 1. Key features of the developed prototype device. (a) Current consumption under different pulse conditions, (b) Comparison with commercial DBS for treating movement disorder

(a)		Polarity	
		Monopolar (anodal)	Even bipolar (anodal)
Duty ratio			
	1/10	47 mA	50 mA
	1/40	45 mA	46 mA

(b)	Symbol	Max. rate	Min. pulse width	Amplitude of stimulation
	Soletra Model 7426 (Medtronic)	185 Hz	$60 \mu\text{s}$	$0 \sim 10.5$ V
	Our system	500 kHz	$1 \mu\text{s}$	$0 \sim 3.3$ V

given patient. Although a more quantitative evaluation of recovery requires a systematic tool, doctors can get basic information about the patient's language and motor abilities through voice communication over the phone and through question-based scoring methods. Actually, we are developing interactive digital devices in tangible forms like PEG board for on-line evaluation of stroke symptoms and recovery progress based on clinically verified scoring and scaling methods (Masur, 2004).

In addition to clinical use in humans, this data mining tool is useful in fundamental research using animal models to investigate the principles of stroke recovery accelerated by cortical stimulation. Moreover, since every individual will have different responses to the electrical stimulation, this data collection approach allows for personalized therapy.

As a conclusion, we have developed a novel electrical neuro-stimulator for stroke recovery on the basis of preliminary experimental results. The ZigBee-based RF communication, stimulation function and internet hookup were successfully integrated in the proposed neuro-modulation system. The precise wireless configuration showed promise for applications such as remote rehabilitation.

With the help of wireless communication, the developed system will facilitate the study of how electrical stimulations affect neural tissues. Currently, the most effective pulse shape parameters for improving stroke recovery are being investigated through animal experiments in collaboration with experts in neurosurgery and neuro-rehabilitation. The site of stimulation is also an important issue for

better efficacy of electric cortical stimulation. Compatibility with magnetic resonance (MR) techniques is another important requirement for the implantable neuro-stimulator because we need to use neuro-imaging systems such as functional MR imaging (fMRI) to study the effect more precisely.

We are also examining additional components including audiovisual support for better treatment or a user-friendly interface especially for patients with severely impaired motor function. The on-line tools for more quantitative evaluation of patient recovery is being integrated into the proposed system for future use, which will be a bi-directional interactive platform for a wide range of tele-rehabilitation techniques.

The system developed here can also be used as a common platform for a wide range of brain diseases and clinical care for which electric stimulation is used.

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