Stochastic stimulation of the motor cortex for treating parkinsonian symptoms: abridged secondary publication

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KEY MESSAGES

1. Stochastic microcurrent stimulation of the motor cortex could ameliorate parkinsonian motor symptoms in the rodent model.
2. The prototype of the cortical stimulator capable of delivering randomised microcurrents was designed and successfully constructed.
3. Refinement in the density of the microelectrodes is expected to improve the efficacy and robustness of the system.
4. The technology has potential in clinical practice in the future.

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Introduction

Parkinson disease is a degenerative disorder of the central nervous system mainly affecting the motor system. It is characterised by movement-related symptoms including resting tremor, rigidity, slowness of movement, and difficulty with walking and gait. Parkinson disease is more common in the older population, and the onset usually occurs after the age of 50 years. In Hong Kong, the number of patients with Parkinson disease is estimated to be more than 10 000.[1] As life expectancy continues to increase, the prevalence of Parkinson disease is projected to surge in the coming decades, resulting in an increase of financial and manpower burden to the healthcare system. To date, there is no known cure for Parkinson disease, but some treatments can reduce neural degeneration in the brain and provide relief from motor-related symptoms. Deep brain stimulation (DBS) involves implantation of stimulating electrode that sends electrical pulses targeting at deep brain structures such as the subthalamic nucleus. DBS is considered an effective neurosurgical procedure in reducing motor symptoms, especially in patients receiving maximum pharmacological treatment.[2] DBS relies on a highly invasive deep brain surgery that sometimes results in infection or intracranial haemorrhage. DBS needs to be guided by intraoperative magnetic resonance imaging for direct visualisation of brain tissue and device, and slightly inaccurate placement of the stimulating electrodes may lead to stimulation of non-target areas and therefore undesirable motor and non-motor adverse effects. Based on our previous findings in experimental animals that DBS could result in the generation of antidromic spikes in the motor cortex,[3,4] we aim to develop a prototype of a multi-electrode stimulating array system capable of delivering controlled microcurrents that are randomised in frequency, amplitude, and pulse width to mimic the antidromic spikes arriving at the motor cortex. We also assessed the therapeutic effect of the stochastic cortical stimulation in ameliorating motor symptoms in a rat parkinsonian model.

Methods

Methods used included: construction of custom-design of the cortical stimulation system, generation of a parkinsonian rat model, implantation procedure of stimulation assembly, and assessment of open-field motor behaviour.

Results

Construction of custom-designed cortical stimulator prototype

We constructed a cortical stimulator capable of delivering controlled microcurrents via 16 independent microelectrodes. The main components include microelectrode array, connecting wire, controller board and software control (Fig. 1).

Stimulus parameters that produced uncontrolled motor activities

In the first stage of experimentation, we identified the set of stimulus parameters that would result in undesirable adverse effects on the tested animals. The Table shows some typical combinations of stimuli parameters tested in parkinsonian animals. Some combination of stimulus parameters could result in the generation of uncontrolled seizure-like activity in over 50% of the animals. Examination of the parameters showed that although there was not

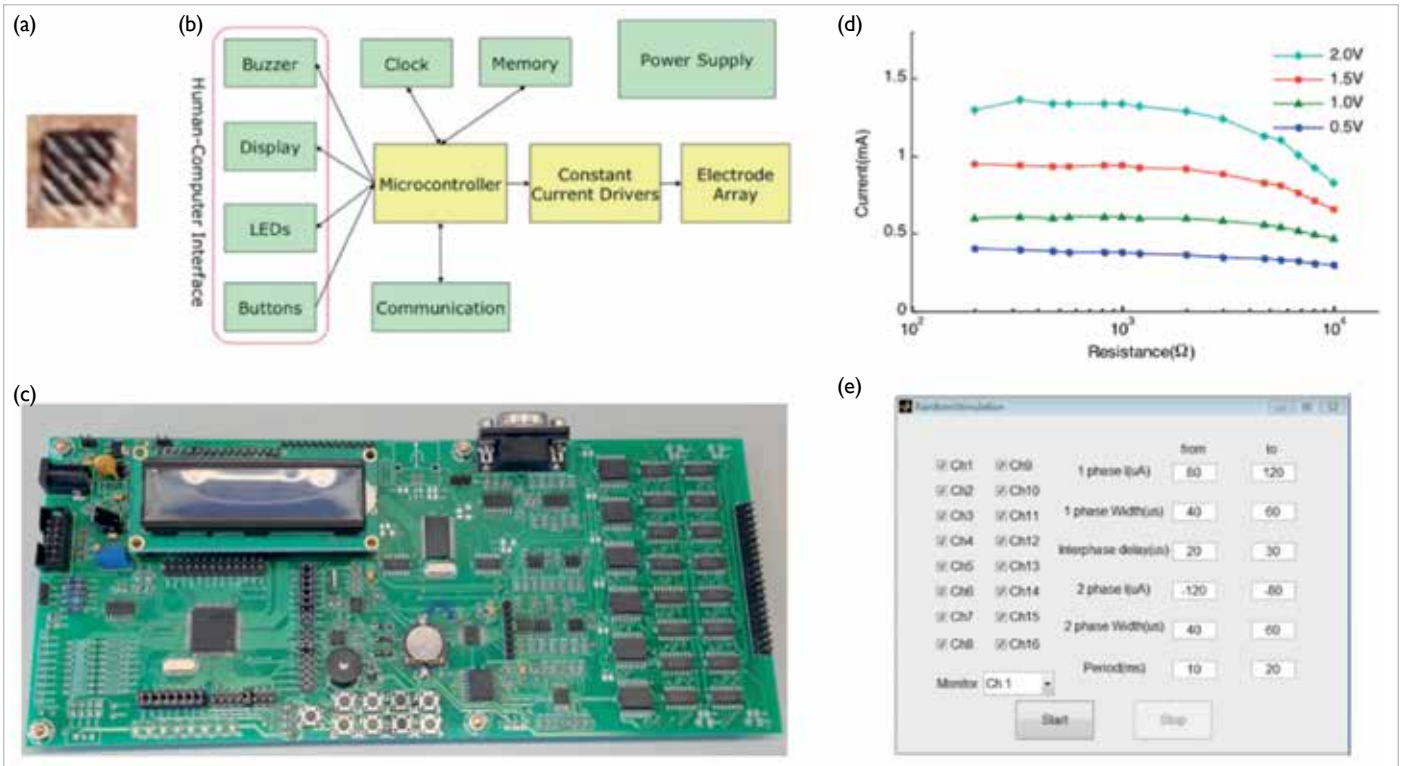

FIG. 1. Prototype of cortical stimulator and controller: (a) The custom-designed and fabricated microelectrode array, (b) the block diagram of the custom-built cortical stimulation controller, (c) the printed circuit board with a 16-channel constant current driver outputting microcurrents to the electrode array, (d) the output performance of the constant current driver at different levels of control voltage, (e) a screenshot of the MATLAB program that sets the location, amplitude, frequency, and pulse width of the randomised microcurrents.

TABLE. Higher values of stimulus parameters can evoke undesirable adverse effects: the highlighted cells are patterns that caused seizures in the Parkinson rat model.

Pulse width, μs	Frequency of the pulse, Hz	Amplitude of the pulse, μA	Pulse width, μs	Frequency of the pulse, Hz	Amplitude of the pulse, μA	Pulse width, μs	Frequency of the pulse, Hz	Amplitude of the pulse, μA	Pulse width, μs	Frequency of the pulse, Hz	Amplitude of the pulse, μA	Pulse width, μs	Frequency of the pulse, Hz	Amplitude of the pulse, μA
30-60	1-30	100-200	60-90	1-30	100-200	90-120	1-30	100-200	120-150	1-30	100-200	150-180	1-30	100-200
30-60	1-30	200-300	60-90	1-30	200-300	90-120	1-30	200-300	120-150	1-30	200-300	150-180	1-30	200-300
30-60	1-30	300-400	60-90	1-30	300-400	90-120	1-30	300-400	120-150	1-30	300-400	**150-180**	**1-30**	**300-400**
30-60	1-30	400-500	60-90	1-30	400-500	90-120	1-30	400-500	120-150	1-30	400-500	**150-180**	**1-30**	**400-500**
30-60	30-60	100-200	60-90	30-60	100-200	90-120	30-60	100-200	120-150	30-60	100-200	150-180	30-60	100-200
30-60	30-60	200-300	60-90	30-60	200-300	90-120	30-60	200-300	120-150	30-60	200-300	**150-180**	**30-60**	**200-300**
30-60	30-60	300-400	60-90	30-60	300-400	90-120	30-60	300-400	**120-150**	**30-60**	**300-400**	**150-180**	**30-60**	**300-400**
30-60	30-60	400-500	60-90	30-60	400-500	**90-120**	**30-60**	**400-500**	**120-150**	**30-60**	**400-500**	**150-180**	**30-60**	**400-500**
30-60	60-90	100-200	60-90	60-90	100-200	90-120	60-90	100-200	120-150	60-90	100-200	150-180	60-90	100-200
30-60	60-90	200-300	60-90	60-90	200-300	90-120	60-90	200-300	120-150	60-90	200-300	**150-180**	**60-90**	**200-300**
30-60	60-90	300-400	60-90	60-90	300-400	**90-120**	**60-90**	**300-400**	**120-150**	**60-90**	**300-400**	**150-180**	**60-90**	**300-400**
30-60	60-90	400-500	60-90	60-90	400-500	**90-120**	**60-90**	**400-500**	**120-150**	**60-90**	**400-500**	**150-180**	**60-90**	**400-500**
30-60	90-120	100-200	60-90	90-120	100-200	90-120	90-120	100-200	120-150	90-120	100-200	150-180	90-120	100-200
30-60	90-120	200-300	60-90	90-120	200-300	90-120	90-120	200-300	120-150	90-120	200-300	**150-180**	**90-120**	**200-300**
30-60	90-120	300-400	60-90	90-120	300-400	90-120	90-120	300-400	**120-150**	**90-120**	**300-400**	**150-180**	**90-120**	**300-400**
30-60	90-120	400-500	60-90	90-120	400-500	**90-120**	**90-120**	**400-500**	**120-150**	**90-120**	**400-500**	**150-180**	**90-120**	**400-500**

a definitive threshold value of either the stimulus frequency, width, or amplitude that would result in epileptic-like activity, a combination of higher values of pulse width (>120 μs) and current amplitude (>300 μA), rather than stimulation frequency, was more likely to generate the undesirable effect.

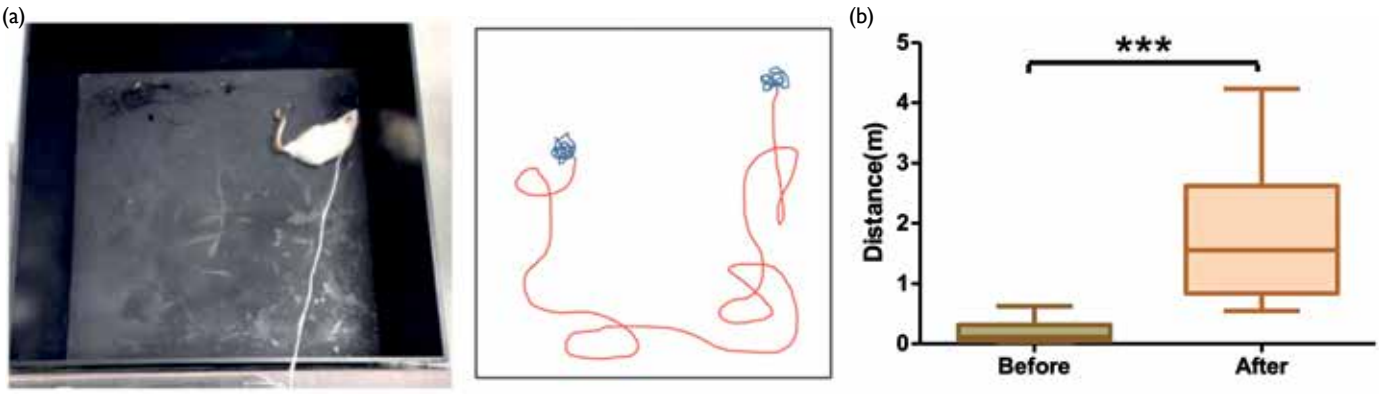

FIG. 2. (a) Some specific patterns of stimulation directly to the rat motor cortex through the connecting cable enable the parkinsonian rat to exhibit more mobile behaviour, travelling more distances in the open arena during stimulation, which is shown by the red tracking line. (b) Comparison of the distances that parkinsonian rats moved 5 minutes before stimulation and 5 minutes during stimulation. The stimulation parameters are amplitude of 100 μA, pulse width of 60-80 μs, and frequency of 30-60 Hz.

Stimulus parameters that ameliorated parkinsonian motor symptoms

Systematically examination of the effects of stimulus parameter combinations on locomotor activity showed that some combinations could improve the mobility of the parkinsonian animals. Confining the stimulus amplitude of the pulse to 100-200 μA, the optimal patterns were pulse width of 60-80 μs and frequency of 30-60 Hz as well as pulse width of 60-80 μs and frequency of 90-120 Hz. Typical examples of the effect of stimulation and statistical evaluation are shown in Fig. 2.

Discussion

Our systematic tests for different combinations of stimulation frequency, pulse width, and amplitude demonstrated that some combinations of these parameters at specific ranges could ameliorate motor immobility of parkinsonian rats. Although the degree of improvement was modest, a significant increase in the distance travelled by the animals was found. Given that stochastic nature of microcurrent delivery aiming to break the pathological synchronised activities of cortical neurons, higher values of current amplitude and pulse width could induce seizures, as too strong stimulation would probably cause excessive excitation of the neurons, regardless of the pattern of stimulation. Although the epileptogenic threshold was not defined by electroencephalographic recordings during stimulation, it was inferred by clear uncontrolled activities of the test subject. Future study should define the epileptogenic threshold by more objective measures such as simultaneous electroencephalographic measurement. It should be pointed out that the optimal effective stimulation frequency is less than that used by the DBS used clinically (ie, 120 Hz). This finding is consistent with our previous discovery that the actual frequency of antidromic spikes generated in DBS is less than the high frequency delivered (ie, 120 Hz). It is likely that the randomised microcurrents at different locations help break the pathological synchronised firing of motor cortical neurons found in parkinsonism.

In this study, we placed a microelectrode array on the cortical surface, rather than deep in the brain, and therefore less invasive to the brain. Less invasive or non-invasive may be a promising direction for Parkinson disease treatment. If the cortical stimulation has equal or better efficacy than DBS, it may replace DBS. In addition, future studies should address the short-term and long-term effects as well as potential interaction with drugs.

Funding

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