RGC Ref.:M-CUHK409/13
(please insert ref. above)

The Research Grants Council of Hong Kong
SRFDP & RGC ERG Joint Research Scheme
Completion Report

(Please attach a copy of the completion report submitted to the Ministry of Education by the Mainland researcher)

Part A: The Project and Investigator(s)

1. Project Title

Elucidating the therapeutic mechanisms of deep brain stimulation in Parkinson's disease by selective in vivo optogenetic manipulation strategy

2. Investigator(s) and Academic Department/Units Involved

	Hong Kong Team	Mainland Team
Name of Principal Investigator *(with title)*	Dr. Wing-Ho YUNG	Dr. Jian-Jun WANG
Post	Professor	Professor
Unit / Department / Institution	School of Biomedical Sciences, CUHK	Dept of Biological Science and Technology, School of Life Sciences, Nanjing University
Contact Information	Room 304, Lo Kwee Seong Integrated Biomedical Sciences Building, Area 39, The Chinese University of Hong Kong	
Co-investigator(s) *(with title and institution)*	Dr. Ya KE, Associate Professor, School of Biomedical Sciences	
PhD student(s) (with period of involvement)	Name: Danny C.W. Chan Institution: School of Biomedical Sciences Period from 1/8/2013 to 31/7/2017	

Note: The Hong Kong project team must involve at least one research postgraduate student pursuing a Doctor of Philosophy degree at the UGC-funded university (PhD student) at any time throughout the project period.

3. Project Duration

	Original	Revised	Date of RGC/ Institution Approval *(must be quoted*)
Project Start date	1.1.2014		
Project Completion date	31.12.2016		
Duration *(in month)*	36		
Deadline for Submission of Completion Report	31.12.2017		

Part B: The Completion Report

5. Project Objectives

5.1 Objectives as per original application

1. To develop a novel in vivo optogenetic stimulation technique using patterned laser light delivery and gradient refractive index optical implants to dissect functional neural circuitry.
2. Using the system, to investigate the possible role of motor cortex interneurons as a previously unknown central mechanism for the therapeutic effects of deep brain stimulation in Parkinson's disease.

3. To quantify the contribution of motor cortex lateral connectivity to the total therapeutic effects of deep brain stimulation.

5.2 Revised Objectives

Date of approval from the RGC: _____

Reasons for the change: _____

_____

1.
2.
3. ....

6. Research Outcome

Major findings and research outcome
(maximum 1 page; please make reference to Part C where necessary)

Under objective 1, we first established a conventional optogenetic system and tested its performance in effective delivery of light to activate virus-mediated expression of channelrhodopsin in the midbrain-motor cortex pathway *in vivo*. Tyrosine hydroxylase promotor driven expression of channelrhodopsin in the midbrain dopamine allows targeting of their terminals in the motor cortex. With optogenetic stimulation, we were able to show that motor learning and motor execution are improved, which complement our electrophysiological investigation of the role of layer-specific synaptic plasticity in the motor cortex. We have then constructed another stimulation system capable for delivering patterned light stimulation, and have tested in in vitro and in vivo condition. The result under in vitro condition is superior than that tested in vivo because there is more constraint in assembly of the mechanical components under in vivo condition. Nevertheless, we have applied the technique in both in vivo and in vitro condition. As mentioned in Objective 1 of the proposal, application of the optogenetic technique could help dissect functional neuronal circuits. We have applied the technique to investigate the role of a cortex-subcortical pathway, namely the prelimbic cortex-nucleus accumbens pathway

in mediating strategy-switching ability in normal and Parkinsonian states. This study had recently been submitted to the *Proceedings of the National Academy of Sciences, USA* and is currently under revision.

For objectives 2 and 3, we have constructed an *in vivo* whole-cell patch clamp setup, and new paradigm on neuron recovery and volume reconstruction that could provide information of recorded neurons in the motor cortex. To study the changes in the neuronal activities of motor cortical neurons in normal and Parkinsonian states, we have compared the membrane excitability and spontaneous synaptic inputs onto the neurons, and discovered changes in both aspects. We have obtained evidence that excitatory synaptic inputs, rather than inhibitory inputs, may be a major manifestation of the Parkinonian pathophysiology, and involved in mediating therapeutic deep brain stimulation. This would argue against our original hypothesis that the interneurons play a critical role in mediating Parkinsonian symptoms and deep brain stimulation mechanism, but nevertheless points to a new direction for future pursuit. Some of these results have been presented in three international meetings overseas.

Potential for further development of the research and the proposed course of action *(maximum half a page)*

The results of the present project represent part of the effort, and an important foundation, of the PI's laboratory to establish innovative technologies to investigate the functions and malfunctions of the nervous system. Future work will continue in this direction.

7. The Layman's Summary

(describe <u>in layman's language</u> the nature, significance and value of the research project, in no more than 200 words)

Development of innovative techniques is important in advancing our understanding of the functions and malfunctions of the nervous system. In this project, we have developed tools for specific manipulations and recordings of neurons to get a better understanding of the cortical origin of the Parkinsonian motor and non-motor symptoms and their rectification by deep brain stimulation.

<u>Part C: Research Output</u>

8. Peer-reviewed journal publication(s) arising <u>directly</u> from this research project

(Please attach a copy of each publication and/or the letter of acceptance if not yet submitted in the previous progress report(s). All listed publications must acknowledge RGC's funding support by quoting the specific grant reference.)

The Latest Status of Publications	Author(s)	Title and	Submitted to	Attached	Acknowledge	Accessible

Year of publication	Year of Acceptance *(For paper accepted but not yet published)*	Under Review	Under Preparation *(optional)*	***(bold** the authors belonging to the project teams and denote the correspondin g author with an asterisk*)*	Journal/ Book *(with the volume, pages and other necessary publishing details specified)*	RGC *(indicate the year ending of the relevant progress report)*	to this report *(Yes or No)*	d the support of this Joint Research Scheme *(Yes or No)*	from the institutional repository *(Yes or No)*
2018 (expected)		Under revision		Qiaoling Cui, Qian Li, Lei Chen, Nancy Y Ip, **Ya Ke*, Wing-Ho Yung***	Dopamine receptors mediate strategy abandoning via modulation of a specific prelimbic cortex-nucleus accumbens pathway. Proceedings of the National Academyc of Science, USA	No	No (under revision, not yet published)	Yes	Not yet
2017	2017			彭荣超,梁拓, **王建军,柯亚, 容永豪***	一种用于大鼠“刺激-奖赏”行为实验的全自动化装置[EB/OL]. 北京：中国科技论文在线 [2017-03-29]. http://www.paper.edu.cn/releasepaper/content/201704-25.	No	Yes	Yes	Yes
2016	2016			**W.H. Yung ***	Plasticity of the motor cortex: focusing on the role of dopamine innervation. Chi. J. Pharmacol & Toxicol. 30(10: 1001-1002	No	Yes	Yes	Yes

9. Recognized international conference(s) in which paper(s) related to this research project was/were delivered *(Please attach a copy of each delivered paper. All listed papers must acknowledge RGC's funding support by quoting the specific grant reference.)*

Month/Year/ Place	Title	Conference Name	Submitted to RGC *(indicate the year ending of the relevant progress report)*	Attached to this report *(Yes or No)*	Acknowledged the support of this Joint Research Scheme *(Yes or No)*	Accessible from the institutional repository *(Yes or No)*
Nov/2014/ Washington DC	Layer specific inputs to layer V primary motor cortex exhibit different profiles of training-induced synaptic plasticity	Neuroscience 2014 - 44th Annual Meeting of the Society for Neuroscience, USA	Yes, Progress report in 2015	No	Yes	Yes
Nov/2014/ Washington DC	Spatial tracking and volume reconstruction for in vivo blind whole cell patch-clamp recordings	Neuroscience 2014 - 44th Annual Meeting of the Society for Neuroscience, USA	Yes, Progress report in 2015	No	Yes	Yes
Nov/2015/C hicago	Neuronal ensemble dynamics in layer 5b of primary motor cortex during motor learning	Neuroscience 2015-45th Annual Meeting of the Society for Neuroscience, USA	No	Yes	Yes	Yes
July/2016/Y okohama	Population dynamics of output layer neurons in motor cortex during motor skill learning	39th Annual Meeting of the Japan Neuroscience Society	No	Yes	Yes	Yes

10. Student(s) trained *(Please attach a copy of the title page of the thesis.)*

Name	Degree registered for	Date of registration	Date of thesis submission/ graduation
CHAN, Danny Cheuk Wing	PhD	1-Aug-2013	Dec 2017

11. Other impact *(e.g. award of patents or prizes, collaboration with other research institutions, technology transfer, etc.)*

This work is in collaboration with Nanjing University and HK University of Science and Technology.