BRAIN

An interdisciplinary joint effort to provide a better understanding of the structure and functions of the human brain and the understanding of mind, including potential of human-machine interfaces.

From Memory Formation to Treatment of Brain Disorders

How memories are formed has long been a fundamental question for neuroscientists. Studies by **Professor He Jufang**, Wong Chun Hong Chair Professor of Translational Neuroscience in the Department of Neuroscience and Department of Biomedical Sciences, have shed light on the crucial role of a key neuromodulator, called cholecystokinin (CCK), in memory forming in the neocortex. As a result of the discovery of CCK's functions, Professor He is developing a treatment strategy to alleviate epilepsy, tinnitus, Alzheimer's disease, and other brain disorders.

Memory is stored in a network of neurons through the persistent changes in the strength of connections between neurons, described as synaptic plasticity. These connections, called synapses, allow neurons to communicate with each other. The strength of communication, called synaptic strength, can be modified, depending on how often these connections are activated. The more active the connections are, the stronger they become. The lasting increase in synaptic strength is called long-term potentiation (LTP). And long-term synaptic plasticity forms the model for memory storage.

Discovery of crucial neuromodulator in memory formation

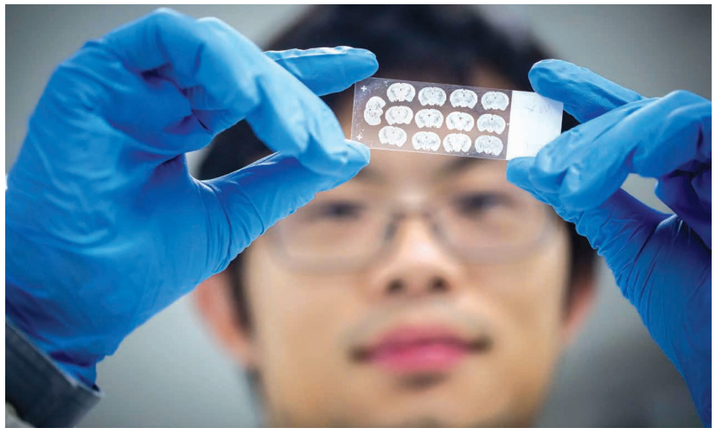
During the communication between two neurons across a synapse, an electric signal is converted into a chemical signal, in the form of neurotransmitter release. Upon binding to the receptor, the transmitter switches back into an electric form travelling through the neuron.

By investigating the chemical composition of dozens of neurotransmitters and neuromodulators in the medial temporal lobe, Professor He and his team discovered that CCK is crucial in switching on memory writing in the neocortex. In particular, they found out how memory is encoded and how visual and auditory inputs are associated.

Subsequently, they found that the N-methyl-D-aspartate (NMDA) receptor, which was once widely recognised as the most important receptor in mediating the formation of memory, actually controls the release of CCK. And it is CCK that induces long-term synaptic plasticity, enabling memory formation.

While their discovery is about memory formation, its implications and application potential extend further. "Epilepsy and many neurodegenerative diseases, such as Alzheimer's, are strongly associated with synaptic plasticity in the brain," said Professor He. "Our findings revealing the relationship among CCK, LTP and synaptic plasticity provide a theoretical basis for developing treatments for different brain diseases."

For instance, they are studying the relationship between high-frequency stimulation-induced LTP in the hippocampus and CCK, and between spatial memory and CCK. In particular, they will examine whether CCK agonists (chemicals act like CCK and therefore stimulate the same receptors) can rescue spatial learning in memory-deficient mice, with the long-term goal of future drug development to help patients with Alzheimer's or neurological disorders retain memory.



Cortical slides of the mice from experiments for studying the formation of memory.

Treatment strategy for tinnitus

The team is also investigating the possibility of treating tinnitus with the administration of CCK4, a type of CCK agonist, paired with sound therapy.

Tinnitus patients hear phantom sounds, like clicking, buzzing or ringing. Tinnitus alone can severely disrupt quality of life. The majority of tinnitus cases occur after patients suffer from peripheral hearing loss because of exposure to either long-term loud noise or a blast. In a fraction of cases, the brain is incapable of compensating for the loss of major ascending cochlear input to the major centres of the central auditory pathway, namely the auditory thalamus and auditory cortex. Neurons that lose cochlear input in these brain regions become hypersensitive and show synchronised activity, called thalamocortical oscillations. This constant activity in the loop can be perceived as a constant phantom sound, tinnitus.

"We plan to apply CCK agonists to patients to activate plasticity in the brain, and then apply sound therapy to rewire synaptic connections in the thalamocortical complex," said Professor He. "The novelty of our approach involves triggering synaptic plasticity in the brain through the administration of CCK4. Preliminary results show a promising outcome."

Application in alleviating epilepsy

Moreover, inhibiting CCK activation may help alleviate involuntary seizures in epilepsy patients.

Epilepsy is one of the most prevalent neurological disorders characterised by spontaneous recurrent seizures. "Anti-epileptic drugs have been used as long-term treatment solutions. But 35% of patients have been found to become resistant to the medication. Temporal lobe epilepsy is one of the most severe and frequent pharmaco-resistant types of epilepsies," explained Professor He.

After having established the link between epilepsy and the strengthening of the neural network with CCK from the medial temporal lobe, the team will explore a treatment strategy by blocking the synaptic strength with CCK receptor antagonists.

Professor He Jufang (back) and his research group members.

Major Award

- The President's Award 2018, CityU

Key Projects

- General Research Fund:
  - A Novel CCK Receptor Regulates the Long-term Potentiation of Inhibition in the Auditory Cortex
  - Cholecystokinin Administration Rescues Thalamocortical Neuroplasticity in Old Rodents
  - GABAergic Cholecystokinin Enhances the Local Inhibitory Effect in the Auditory Cortex
- Health and Medical Research Fund:
  - Neuroplasticity Induced by the Administration of Cholecystokinin Tetrapeptide and Noise Exposure as a Novel Strategy for the Treatment of Tinnitus
  - The Development of Upconversion-based Wireless Optogenetics as an All-optical Therapeutic Strategy to Study and Treat Parkinson's Disease
- Innovation and Technology Fund:
  - Assay Platforms for CCK-B Receptor Agonists as Potential Treatment for Amnestic Mild Cognitive Impairment

Selected Publications & Patents

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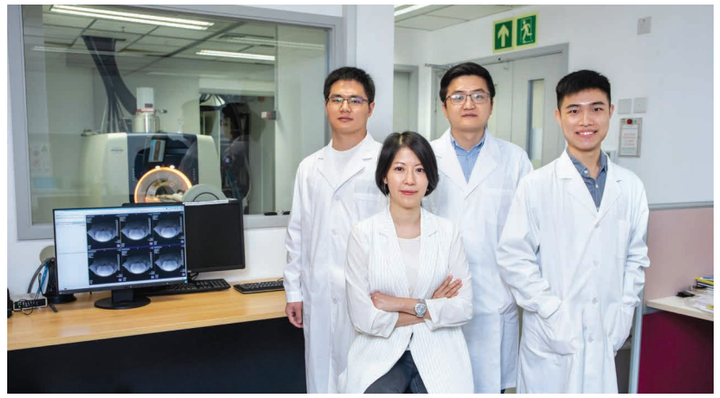
New MRI Approach for Earlier Detection of Alzheimer's Disease



Dr Kannie Chan Wai-yan (first row) and her research team.

Collaborative research by CityU and Johns Hopkins University has developed a new, non-invasive way to identify Alzheimer's disease even before any symptoms appear.

Dr Kannie Chan Wai-yan, Associate Professor in the Department of Biomedical Engineering (BME) at CityU, and her team collaborated with scientists from the US, Sweden and Hong Kong in pioneering this pre-clinical study. They developed a molecular imaging approach, based on Magnetic Resonance Imaging (MRI), to dynamically measure glucose level changes in the brain's lymphatic system, which can provide early cues about the disease. Their findings were published in the scientific journal *Science Advances* in May, 2020.

"The tricky part of fighting Alzheimer's disease is that early symptoms, such as the emergence of protein plaques in the human brain, which hamper the cognitive function, are similar to normal ageing," said Dr Chan. "Even more challenging, patients diagnosed with symptoms are most likely in the middle or late stage of the disease. Overlooked pathologies in the brain could have happened 15 or 20 years before the symptoms appear."

Dr Chan's team's new imaging approach can assess glucose uptake and clearance in the lymphatic system of the brains of mice in a non-invasive way. "By using glucose as a natural 'tracer', our imaging method can sensitively detect the distinctive changes in the lymphatic system function at the molecular level at the early stage of Alzheimer's disease, helping us to differentiate it from normal ageing," she said.

The new imaging approach is compatible with the MRI machines commonly used in clinics and hospitals, which means low set-up cost and technically easy transfer to clinical applications. Dr Chan anticipates that clinical trials can be conducted within three years.

Major Awards

- Young Investigator Award, Overseas Chinese Society for Magnetic Resonance in Medicine, 2020
- ISMRM Magna cum Laude Merit Award 2020
- Teaching Excellence Award 2020, CityU

Key Project

- General Research Fund: Development of Theranostic Hydrogels for MRI-guided Brain Tumor Treatment

Selected Publications

- Huang, J., Chen, L., Xu, X., van Zijl, P.C.M., Xu, J. & **Chan, K.W.Y.** 2020, "Multi-slice nuclear overhauser enhancement imaging with suppressed magnetization transfer for hydrogel-based therapy in the brain at 3 T MRI", *Magnetic Resonance in Medicine, (in press)*.
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Discovering the Neural Mechanisms Between Chronic Pain and Cognitive Deficits

Having developed dynamic schema-like memory consolidation, it only took the rat one training session to find the correct food location from the sand well.

While the clinical connection between chronic pain and increases in levels of anxiety, depression, cognitive dysfunction has long been established, the underlying mechanisms of brain neural networks remain less understood. **Professor Li Ying**, Chair Professor in the Department of Neuroscience and Department of Biomedical Sciences, has achieved breakthroughs by unveiling the secrets of brain molecules and tissue – astrocytes and myelin – in the central nervous system. By identifying the roles of astrocyte lactate signalling and myelin plasticity in circuitry synchrony, he has shed light on how fundamental cognitive functions, including learning, memory and decision-making, could be rescued and enhanced, especially for patients suffering from chronic pain.

Astrocytes, which are star-shaped glial cells in the anterior cingulate cortex (ACC), are crucial in influencing neuronal functions. Professor Li and his team found that during synaptic activity (when an electrical or chemical signal is passed from one neuron to another or to a target effector cell), astrocytes release a substance called L-lactate, which is utilised by neurons to promote information flow and synchrony in the brain neural circuitry, thereby improving decision-making performance.

L-lactate: a signalling molecule to improve decision-making

Recently L-lactate has been recognised as an important fuel for many cells. But Professor Li's study found another essential role: as a signalling molecule in neuronal activity plasticity and neuronal network synchrony in the brain.

Using the previously established "chronic visceral pain rat model", the research team found that L-lactate infusion into the ACC increased the proportion of good decisions by normal rats by up to 48% and significantly relieved decision-making dysfunction in rats with chronic visceral pain. The animal experiments support the idea of an "astrocyte-to-neuron L-lactate shuttle", which means that the exogenous administration of L-lactate or optogenetic activation of astrocytes can stimulate astrocytes in abnormal neural circuitry and may help alleviate cognitive deficits caused by chronic pain.

Apart from investigating the pathological mechanisms of pain-related brain disorders for years, Professor Li was also the first to decipher the critical role of myelin in advanced cognitive memory and how its growth and regeneration can be fostered to enhance the synchrony of neural networks and improve cognitive functions.

The critical role of myelin in cognitive functions

Myelin, or myelin sheath, a multi-layered fatty tissue wrapped around neuronal axons, insulates and protects neurons, and increases the rate at which information is passed along the axons. Its formation is controlled by oligodendrocytes, which are large glial cells in the central nervous system.

The team discovered that schema-like learning, which is learning through repetition, can foster the growth of brain myelin. Memory schemas have been introduced to cognitive psychology to understand how new information is integrated with pre-existing knowledge. So the team applied schema-like learning to design the study of behaviour in rats.

In weeks of training, the rats learned multiple types of flavour-place paired association, so that they could remember which kind of food was hidden in which sand well. After training, when the rats smelled a certain kind of food, they could quickly go to the correct sand well and dig it out, showing that they had developed dynamic schema-like memory consolidation and retrieval. When the rats were introduced with two new flavour-place pairs, it only took them one training session to find the correct food location, indicating that the integration of new information into established knowledge progressed very rapidly.

By analysing the changes in the rats' brains with immunohistochemistry and a transmission electron microscope, the researchers found that the myelin of the ACC of the trained rats had grown substantially in the process of learning and developing memory schema.

In addition, the team reversely demonstrated the importance of myelin in enhancing learning and memory capacity by interrupting its growth.

By injecting drugs for demyelination in rats, they concluded that the interference of myelin formation can severely disrupt the creation of memory schemas and new memories. The transmission of information within neural circuits and the synchrony of neural networks are negatively affected as well. They also found that myelination is a key factor in facilitating long-range oscillations and synchronisation of spike time arrival between neurons in different brain areas.

"With the use of cutting-edge optogenetic, chemogenetic and pharmacological technologies, we can precisely control brain oligodendrocytes to promote myelin formation," said Professor Li. "We will explore whether these methods can improve severe cognitive impairment caused by central myelin diseases such as severe depression, chronic recurrent pain, irritable bowel syndrome, and Alzheimer's disease."

He and his team will continue to investigate neural network synchronisation to identify the causality of chronic pain and associated cognitive deficits, which will lay the groundwork for developing effective treatment and prevention strategies.

"Neuroscience is a complex discipline, which covers a broad base of life sciences, and is related to other disciplines, such as physics and information technology. So we should expand our knowledge in all these fields. There is also a crucial connection between philosophy and cognitive science. The driving forces of hypotheses and advanced biotechnologies should be used in concert to explore the beauty of the philosophy of mind and cognition."

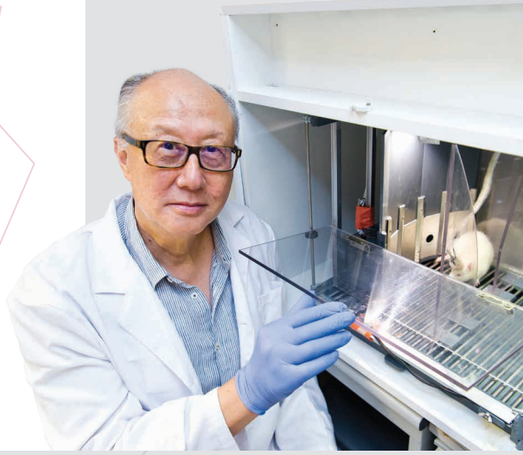
- Professor Li Ying

Major Awards

- Fellow, American Gastroenterological Association
- Guest Principal Investigator: Institute of Brain Cognition and Brain Disease, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences

Key Projects

- General Research Fund:
  - Chronic Pain Induces Hypomyelination: A Causal Mechanism for Brain Circuitry Desynchronization and Impaired Decision Making
  - Impairment of Schemas and Memory Consolidation and Disruption of Schemas-linked Interactions Between Hippocampal and Anterior Cingulate Cortex in Chronic Visceral pain
- NSFC/RGC Joint Research Scheme: L-lactate Release by Optogenetic Activation of Astrocytes Rescues Decision-making Deficit in Visceral Hypersensitive Rats
- Health and Medical Research Fund: Impaired Communications in Anterior Cingulate Cortex Neural Network in the Rats with Trigeminal Neuropathic Pain is Associated with Decision-making Deficits



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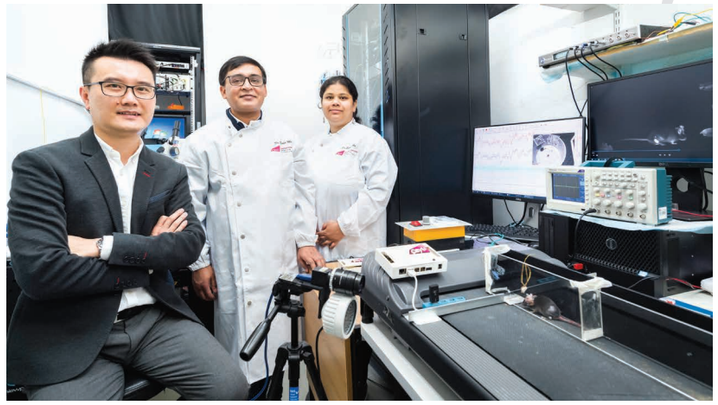
Novel Neural Prosthetic Devices for Neurodegenerative Diseases

Patients suffering from spinocerebellar ataxia (SCA) and Parkinson's disease (PD), two incurable neurodegenerative diseases, often experience problems with movement and motor coordination. **Dr Eddie Ma Chi-him**, Associate Head and Associate Professor in the Department of Neuroscience and Director of the Laboratory Animal Research Unit (LARU) at CityU, is currently developing novel neural prosthetic devices that could improve patients' motor symptoms and improve their quality of life.

Neurodegenerative diseases occur when neurons in the brain or peripheral nervous system lose function over time and ultimately die. Dr Ma, who specialises in studying the intrinsic molecular machinery for central and peripheral nervous system regeneration after injury, has adopted a multi-disciplinary approach spanning electrophysiology, molecular biology, anatomy, animal behaviour and genetics, and is working on advancing deep brain stimulation (DBS) treatment strategies to better assist patients with SCA or PD.

SCA refers to a group of genetic, progressive neurodegenerative disorders, characterised by the loss of body balance, motor coordination, speech and oculomotor difficulties, which affect five per 100,000 people worldwide. Scientists have long recognised the importance of cerebellum, which is the balance and fine movement coordination centre of the brain, as a target site for DBS in the treatment of SCA.



Dr Eddie Ma Chi-him (left) and his research team.

Closed-loop DBS to avoid side effects

"However, conventional open-loop DBS involves continuous and excessive brain stimulation, which has undesirable side effects. It also reduces the battery lifetime of deep brain stimulators, which increases the frequency of replacement surgery. It is estimated that over 50% of continuously delivered stimulation via open-loop DBS in PD patients is unnecessary and can be avoided by using a feedback biomarker, as in closed-loop DBS," explained Dr Ma.

To avoid excessive stimulation, he and his team designed a "closed-loop" deep cerebellar nuclei (DCN) stimulator prototype, which is triggered only when a symptomatic electromyography in the muscle is detected.

The research team is now testing the therapeutic potential of this stimulator prototype in genetically engineered mice with ataxia phenotype. They will first perform electromyography to record muscle activity and video kinematics at different stages of locomotion, and simultaneously record neural activities of DCN in the cerebellum to define symptomatic electromyography activity as a feedback biomarker for closed-loop DBS.

In collaboration with **Dr Tin Chun** in the Department of Biomedical Engineering, Dr Ma and his team will develop a real-time field-programmable gate array (FPGA) algorithm, targeting interposed nucleus of the DCN to close the loop in ataxia mice. The FPGA system is designed to perform complex computations in real time, completing one-second real-world activities within milliseconds. After carrying out further electrophysiology and motor behavioural assessments, the team expects the motor deficit in SCA mice to improve after DBS and the new device to become more durable, resulting in fewer side effects.

New stimulation target site for treating Parkinson's disease

Another research focus of Dr Ma is PD, the second most common chronic neurodegenerative disorder, which affects more than 6.1 million of the world's population and about 1.7% of people aged 60 years or over in China.

Conventional DBS implantation is performed in the ventral intermediate nucleus (VIM) of the thalamus, subthalamic nucleus or globus pallidus interna to modulate either a direct or indirect pathway of the thalamo-cortical-striatal loop. The imbalance between direct and indirect pathways results in abnormal activation of output nuclei and over-inhibition of the thalamus and motor cortex, leading to undesirable side effects, such as cognition impairment, depression and anxiety.

Considering that i) striatum nuclei are the motor integrating centre in the brain modulating both direct and indirect pathways; and ii) the abnormal local field potential (LFP)-beta power and neuronal firing pattern detected in the striatum nuclei of PD patients is associated with motor dysfunction, Dr Ma is exploring striatum nuclei as a novel target site for DBS. His research team has demonstrated that DBS at the striatum nuclei is more effective than DBS at the subthalamic nucleus and globus pallidus interna in improving motor symptoms in two mouse models of PD.

The research team will optimise the DBS parameters so that it is triggered only when a symptom-related biomarker is detected. In collaboration with a US-based company, the optimised therapeutic DBS parameters will be used to develop an implantable microchip prototype of a closed-loop deep brain stimulator using striatum nuclei as a novel DBS target site.

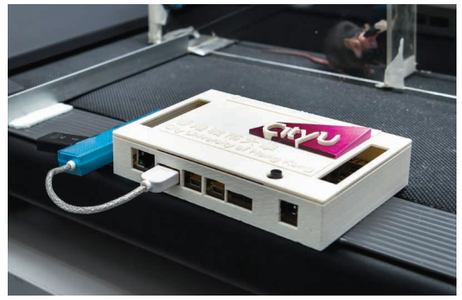
"We believe that the success of the current study will not only minimise side effects in conventional DBS with a new DBS target site, but also take DBS development to the next level by closing the loop. Our closed-loop prototype could minimise unnecessary stimulation in SCA and PD patients to reduce side effects for early intervention," said Dr Ma.

Major Awards

- World Cultural Council Special Recognition, 2018
- The President's Award 2016, CityU
- Croucher Foundation Fellowship 2005-2007

Key Projects

- Innovation and Technology Fund:
  - Therapeutic Potential of a Novel Deep Brain Stimulation Target Site and Neural Prosthetic Device for Treating Parkinson's Disease
  - Therapeutic Potential of Neural Motor Prostheses Device for the Treatment of Spinocerebellar Ataxia



The closed-loop deep brain stimulator prototype developed by Dr Ma's research team.

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- **Ma, C.H.E.** & Au, N.P. B., "Targeting mitochondrial dynamics by mitochondrial fusion promoter M1 as a treatment strategy for nervous system injury," US patent 63/081,371, filed 2020.
- **Ma, C.H.E.**, & Au, N.P. B., "Therapeutic potential of glycopyrrolate and mexiletine for nervous system injury", US patent 63/078,395, filed 2020.
- **Ma, C.H.E.**, Kumar, G., & TIN, C., "Neurostimulation system and method for modulating abnormal motor movement", US patent 16/454,121, filed 2019.