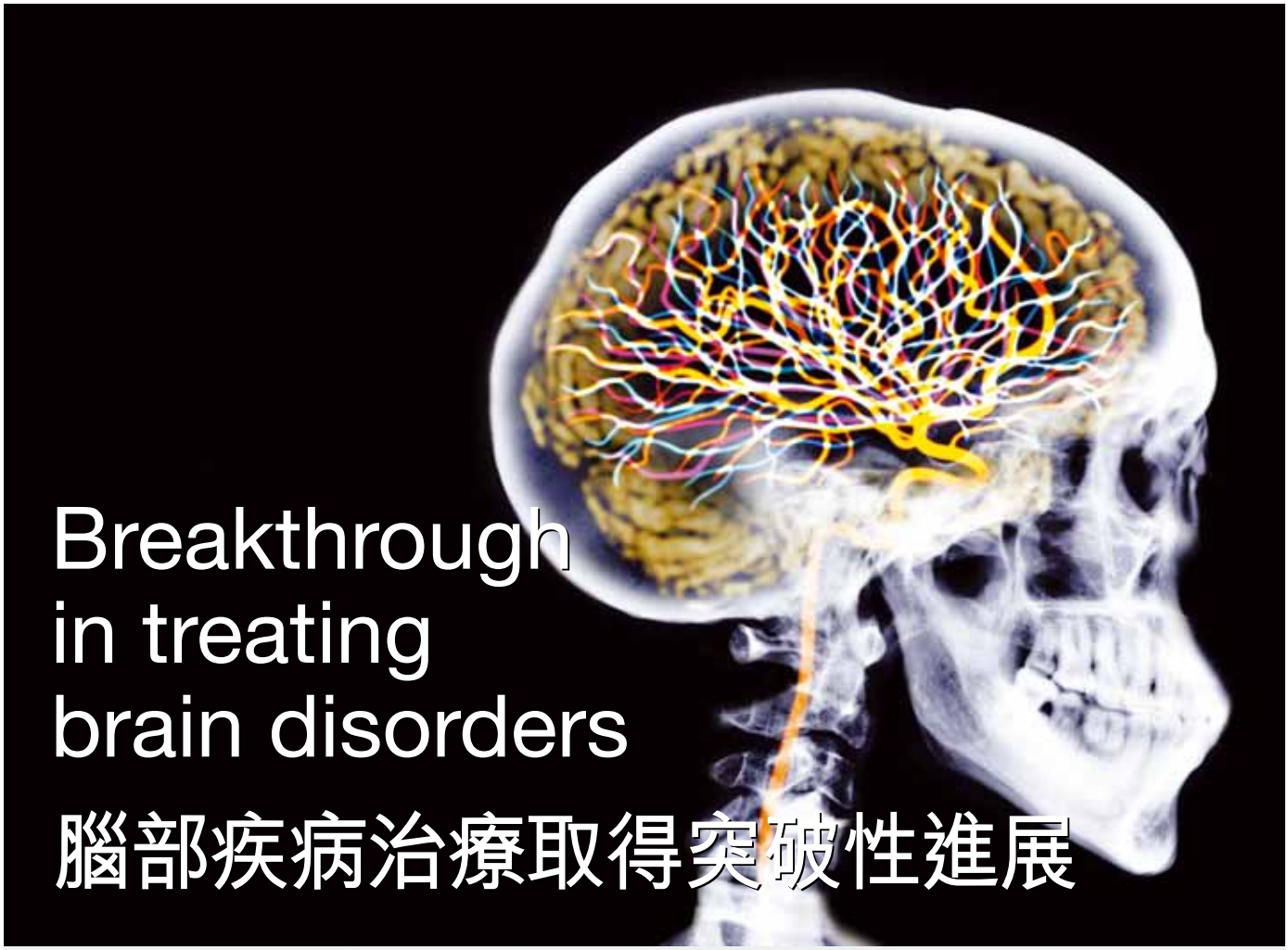


Breakthrough in treating brain disorders

腦部疾病治療取得突破性進展

For long, scientists around the world have been trying to resolve the mystery of the brain, and the causes of the various brain-related health problems such as Alzheimer's disease. In recent years, PolyU researchers have made headway in unlocking part of the mystery.

Lack of effective drug for soaring neurodegenerative disorders

Years before Alzheimer's disease (AD) caught wide public attention as a common problem among the elderly, notably after the revelation of Nobel Laureate Prof. Charles Kao being afflicted with it, Prof. Han Yifan from the Department of Applied Biology and Chemical Technology had embarked on his journey in search of solutions to the progressive brain disorder.

一直以來，全球科學家試圖破解人腦的奧祕，以及剖析各種與人腦有關的疾病（如老人癡呆症）之成因。近年，理大的科研專家在這方面的研究進展理想，正逐步解開部份人腦之謎。

神經退行性疾病急增　卻欠有效治療藥物

老人癡呆症（或稱老人失憶症）這疾病在長者中極為普遍，尤其在諾貝爾獎得主高錕教授被披露患有此症後，更廣為各界關注。其實在多年前，應用生物及化學科技學系韓怡凡教授已開展有關研究工作，尋求可治療這腦部疾病的藥物。

The novel dimer is derived from Chinese herb "Qian Ceng Ta".
新型雙聯體衍化自中草藥「千層塔」。

The veteran researcher in Chinese herbal medicine set his sight on AD back in the 1980s, a time when little attention was paid by governments and the academic arena to the degenerative disorder. "People did not have as long a life expectancy as they do today," said Prof. Han. Nowadays, the disease that causes problems to a person's higher brain functions, memory, thinking and emotions is plaguing tens of millions of people around the world, as the fourth leading cause of death in the developed world, after cancer, heart disease and stroke.

The chance of a person developing AD rises sharply after he/she reaches the age of 65; half of those aged 85 will contract the disease exhibiting such symptoms as memory loss, insomnia, delirium and even inability to take care of oneself. Among the four top killers, AD incurs the most medical costs due to the lengthy period a patient can live with it, says Prof. Han, a former neuro-pharmacology scientist in the US.

Besides the Nobel Laureate Prof. Charles Kao, the late former US President Ronald Reagan and former British Prime Minister Margaret Thatcher are also known victims. Yet in Hong Kong, people tend to have limited understandings if not misunderstandings about the disease despite the rising public attention it has received. In March 2010, Department of Health revealed a survey showing over 15 percent of the 760 respondents thought that they would feel being looked down upon if a family member had dementia. The study also found that many did not know that demented patients, apart from memory loss and decreased cognitive ability, would suffer from other mood, psychological and behavioural problems.

韓教授是資深的中草藥研究專家，他於八十年代開始探究老人癡呆症，但當時各地政府及學術界均對這神經退行性疾病不甚關注。韓教授表示：「與現時相比，那年代的人的平均壽命比較短。」現時，這疾病正折磨全球數千萬人，對他們的高級腦功能、記憶、思維及情緒構成影響，並在發達國家中繼癌症、心臟病及中風後，高據致命疾病的第四位。

當人活到六十五歲，老人癡呆症的發病率就會急劇上升；半數八十五歲的長者更出現記憶力衰退、失眠、精神錯亂及喪失自我照顧能力等老人癡呆症狀。曾在美國研究神經藥理學的韓教授表示，在首四種致命疾病中，醫治老人癡呆症所需的費用最高昂，因為病者可能患上此症後，仍然活着一段很長的時間。

除諾貝爾獎得主高錕教授之外，美國已故前總統列根及英國前首相戴卓爾夫人也是老人癡呆症的受害者。在香港，雖然公眾對這疾病的關注程度已有所提升，但對它的認識仍然有限，甚至存在誤解。根據衛生署於二零一零年三月公佈的一項調查顯示，在七百六十位受訪者中，超過一成半人認為家中若有癡呆症患者會被人歧視。調查亦發現，很多人並不了解癡呆症患者除了記憶及認知能力衰退外，還會有其他情緒、心理及行為等問題。

In the research, this "water maze" is used in animal memory test.
該研究利用「水迷宮」實驗設施，測試動物的記憶力。

Prof. Han (right) and his research team at work.
韓教授(右)及其團隊致力有關研究。

Prof. Han Yifan
韓怡凡教授

East meets West in fighting against AD

Dedicated to combining the best of Western and Eastern medicine to prevent and treat the brain disorder, Prof. Han has finally seen encouraging progress in his experimental work. Based on his past research work which led to the development of dimers (compounds formed by the union of two simpler fragments or molecules), his research team has successfully developed several new dimers that are highly promising drug candidates, derived from homo- or hetero-dimers of tacrine (an approved anti-AD drug that can significantly improve memory and general intellectual functions, but with serious side effects) and/or Huperzine A, a novel alkaloid discovered from the Chinese herb Qian Ceng Ta. These new dimers show memory enhancement and anti-stroke activity in animal models.

"For many years clinical tests have proven Chinese medicine to be useful for slowing down memory decay or enhancing memory process. What we managed to do was identifying and optimizing the right chemical compounds that could help fight the disease," said Prof. Han.

The new dimers can provide double neuroprotection. On one hand, in contact with the nerve cell surface, the dimers can block the N-methyl D-aspartate receptor (NMDAR) for protection against AD. In addition, after the dimers enter the nerve cell, they will further inhibit the nitric oxide synthesis, thus slowing down the development of AD. The promising potentials of the new dimers, possessing both acetylcholinesterase (AChE) inhibition and NMDAR blockade, have been published in more than 50 papers in international academic journals such as *Molecular Pharmacology* and *Journal of Biological Chemistry* over the past few years. Last October, Prof. Han presented the findings at the International Functional Food Symposium hosted by PolyU.

中西合璧抗老人癡呆症

韓教授一直鑽研糅合中西醫藥來預防及治療腦部疾病，經過多年的努力，他的研究終見突破性進展。建基於過往研發二聚體（即由兩種基本分子結合而成的化合物）的研究工作，韓教授的研究團隊成功研發出幾種具有良好療效的新型二聚體。這些二聚體由同源或異源雙聯體他克林（一種具嚴重副作用，但已確定對治療老人癡呆症、改善記憶力及一般智力功能很有成效的藥物）及/ 或石杉鹼甲（從中草藥「千層塔」中提取出來的生物鹼）結合而成。動物實驗結果顯示，這些新型二聚體能有效提升動物的記憶力及預防中風。

韓教授稱：「多年來，臨床醫學實驗已證實中藥有助減慢記憶力衰退或可增強記憶，我們亦已尋找到，並不斷優化合適的化合物來對抗這疾病。」

The way forward in developing a safer drug

Much more work will be done by his team, drawing on the support of the Research Grants Council in Hong Kong, the "973 Program" of the Ministry of Science and Technology of China and the National Science Foundation of China. Prof. Han, a pharmacy graduate of the Shanghai Medical College (now part of Fudan University) said, "We are carrying out in-depth study at the cellular, molecular level as well as in animals, on what, how and why chemicals can protect nerve cells from aging and death. We are further optimizing and working on derivatives from natural compounds to see how they can reduce memory impairment and promote the nerve cells to fight against chemical damage."

Prof. Han's project is also being backed by the Shenzhen Bureau of Science, Technology and Information and he was named a recipient of the Bureau's Hundred Outstanding Scientists Award. "We always like to have more funding support because it is truly very expensive research and it is very important to find a more effective and safer drug for AD. Western medicines have not produced any cure for it yet."

He concedes, however, even should a promising drug be developed, it could be a decade or more before a cure for AD can be identified, due to the time involved in carrying out drug safety and clinical tests.

Prof. Han committed himself to AD research after being struck by the changes of his former "energetic and brilliant" teacher at Shanghai Medical College, who fell victim to the disease. "He could not recognize his students and family members. I was very astonished to see a person of such high level of intelligence and charisma becoming someone who could not remember anything. I wanted to help people like him. The victims of the disease can be moody, frustrated, confused, or lose temper easily."

The novel dimers with low side effects developed by Prof. Han and his research team have opened the door to new prevention and treatment methods for neurodegenerative disorders, such as AD, Parkinson's disease and stroke.

"The American scientific community declared the last decade of the last century as the decade of the brain. Indeed, the coming decades can be called the same. Brain research is a big challenge as more people are living longer and getting brain-related disorders including Alzheimer's disease," added Prof. Han.

Prof. Han's (first from left) research projects are often supported by the Research Grants Council.
韓教授(左一)的研究課題屢獲研究資助局的支持。

嶄新的二聚體可發揮雙重保護神經的作用。當這些二聚體接觸到神經細胞膜時，會阻斷谷氨酸受體產生神經保護作用。另一方面，當二聚體進入細胞後，它們又抑制一氧化氮合成酶產生化學作用，從而減緩老人癡呆症之發展。新型二聚體能同時抑製乙酰膽鹼酯酶及N-甲基-D-天冬氨酸受體活性，這些突破性發現近年已被整理成五十多篇論文，分別發表於《分子藥理學》及《生物化學》等國際學術刊物。去年十月，韓教授亦於理大主辦的國際功能食品研討會上發表有關研究報告。

研發高安全性藥物的前景

在香港研究資助局、中國內地科學技術部「973項目」及中國自然科學基金的支持下，韓教授的研究團隊將持續鑽研有關項目。在上海醫學院（現附屬復旦大學）藥劑學畢業的韓教授表示：「我們正進行細胞及分子層面的深入研究，並利用動物測試那些化學物如何及為何能保護神經細胞，以免細胞老化及死亡。我們又正修改及研究天然複合物的衍生物，探討它們如何減低記憶力衰退，以及幫助細胞對抗因化學物而造成的損害。」

相關的研究計劃亦獲得深圳市科技和資訊局的支援，韓教授更榮獲該局頒授「百位傑出科學家獎」。他表示：「這是一個牽涉巨額經費的研究項目，所以我們渴望得到經費上的資助。研發一種更安全而有效對抗老人癡呆症的藥物是非常重要的，因為現時仍沒有西藥可治癒此病。」

韓教授坦承，由於進行藥物安全及臨床測試需時，所以即使研發出具有良好療效的新藥，仍可能需要用上十年或更長時間來確定治癒老人癡呆症的方法。

韓教授在上海醫學院求學時期，有一位活躍及聰穎的恩師，其後他親眼目睹這位老師患上老人癡呆症後的轉變，大感詫異，因此立志研究該疾病。「老師發病後甚至認不出學生及家人，一個原本才華橫溢和充滿魅力的人竟然甚麼也記不起，這實在令我感到非常驚訝。我希望能夠幫助像他一樣被這病折磨的受害人，他們可能會情緒不穩、常有挫敗感、思緒混亂或容易暴躁。」

韓教授與研究團隊研發的新型二聚體對人體的副作用較少，無疑為探究預防及治療老人癡呆症、柏金遜症及中風等神經退行性疾病的新方法，打開邁向成功的一扇門。

韓教授更表示：「美國科學界宣稱上一個世紀的最後十年為『腦世代』，我則認為未來的數十年都可稱為『腦世代』。隨着人類的壽命越來越長，而又越來越多人患老人癡呆症等腦部疾病，有關腦的研究確實是一項重大挑戰。」

Detection mechanism in the gateway to the cerebral cortex

The work of other PolyU scientists has also contributed to a better understanding of possible ways to tackle brain-related disorders. A research team led by Prof. He Jufang, coordinator of PolyU's Applied Neuroscience Laboratory under the Department of Rehabilitation Sciences, discovered a previously unknown feature of the human brain – the novelty detection mechanism in the gateway to the cerebral cortex – that has implications for the treatment of tinnitus and hyperactive disorder. The research finding was published in the prestigious *Nature Neuroscience* magazine in September 2009.

A joint effort with the Chinese Academy of Sciences (CAS) Institute of Biophysics, the research came out of the partnership between CAS and PolyU on the investigation of visuo-auditory integration. The project was supported by a CAS-Hong Kong Joint Laboratory Grant from the Croucher Foundation and funding from National Outstanding Young Persons Foundation (Category B) of the National Natural Science Foundation of China. Prof. He is the principal investigator for both grants.

In the study, Prof. He's team found that the thalamic reticular neurons as the guardian of the gateway to the cerebral cortex responded to novel stimulus a lot better than to repeated stimulus. "For the past 25 years, scientists have suspected such a mechanism exists, but it was very difficult to prove it," said Prof. He, who was named a Croucher Senior Research Fellow in 2009.

通向大腦皮層的偵測機制

其他理大科學家的科研工作，亦讓人們對治療腦部疾病的療法有更多的認識。理大康復治療科學系賀菊芳教授領導的應用神經科學實驗室發現了人類大腦的一項特徵——通向大腦皮層的獨特偵測機制，該研究有助治療耳鳴及過度活躍的問題。研究結果已刊載於二零零九年九月號的《自然神經科學》期刊。

這項由理大與中國科學院（中科院）生物物理研究所聯合進行的研究，獲裘槎基金會中科院—香港聯合實驗室，以及國家自然科學基金委員會的國家傑出青年基金（B類）資助，賀教授是該兩項資助的首席研究員。這項目旨在探討視覺與聽覺整合的議題。

賀教授的研究團隊發現，負責看守大腦皮層的丘腦網狀神經元，對於新刺激的反應遠超重複刺激的反應。賀教授說:「過去二十五年，科學家已估計有這樣的一個獨特機制，只是很難加以證實。」賀教授於二零零九年獲裘槎基金會頒發優秀科研者獎。

His team used rats in their experiments, in which the animals were presented repeatedly with a two-tone melody, the sound of which pitched mostly at a standard frequency and occasionally at a deviant frequency. This oddball procedure showed that the auditory sector of thalamic reticular neurons – which are inhibitory and control the ascending sensory information in the thalamus – has a deviance preference. Because of that, the brain is apparently tuned to respond to new, rather than repeated stimuli.

Malfunction of mechanism leads to disorders

Prof. He, who supervises doctoral students in CAS-Hong Kong Joint-Laboratory for Visuo-Auditory Integration of the Institute of Biophysics in Beijing, attributes the phenomenon of tinnitus, in which a person is interfered by sounds despite the absence of external stimuli, to the malfunctioning of the specific neurons. “They are supposed to have an inhibition function, that is telling the thalamus to keep quiet, but if they become too weak, the thalamus and the cortex will oscillate, causing the person involved to hear sounds.”

The finding has advanced the understanding of the potential roles of neurons and the mechanism in attention shift, which could happen across sensory modalities. Malfunction of these neurons might cause attention deficit disorders. “It is very likely that people with problems in the neurons will have attention problems. For example, children may have hyperactive disorder and become easily affected by some new stimulus when the structure becomes weak and too sensitive to external stimuli. It is not good if the structure becomes too sensitive.”

Prof. He’s 10-member laboratory is engaged in projects aimed at providing relief for people with different needs or impairments. One successful outcome is the development of “Electronic Bat Ears” for the visually impaired. Having put on the small equipment for 10 minutes, its wearers can navigate their way through a corridor successfully by relying on auditory input, just as in the case of bats. “We tried to mimic the bats which cannot see at night but have two “big ears” to “hear” what is in front,” said Prof. He. Recently, his team has secured funding for a group project from the Research Grants Council to further look into what really goes on in the subjects’ brain after they have put on the equipment, or more precisely, what help them generate a mental image of the surrounding.

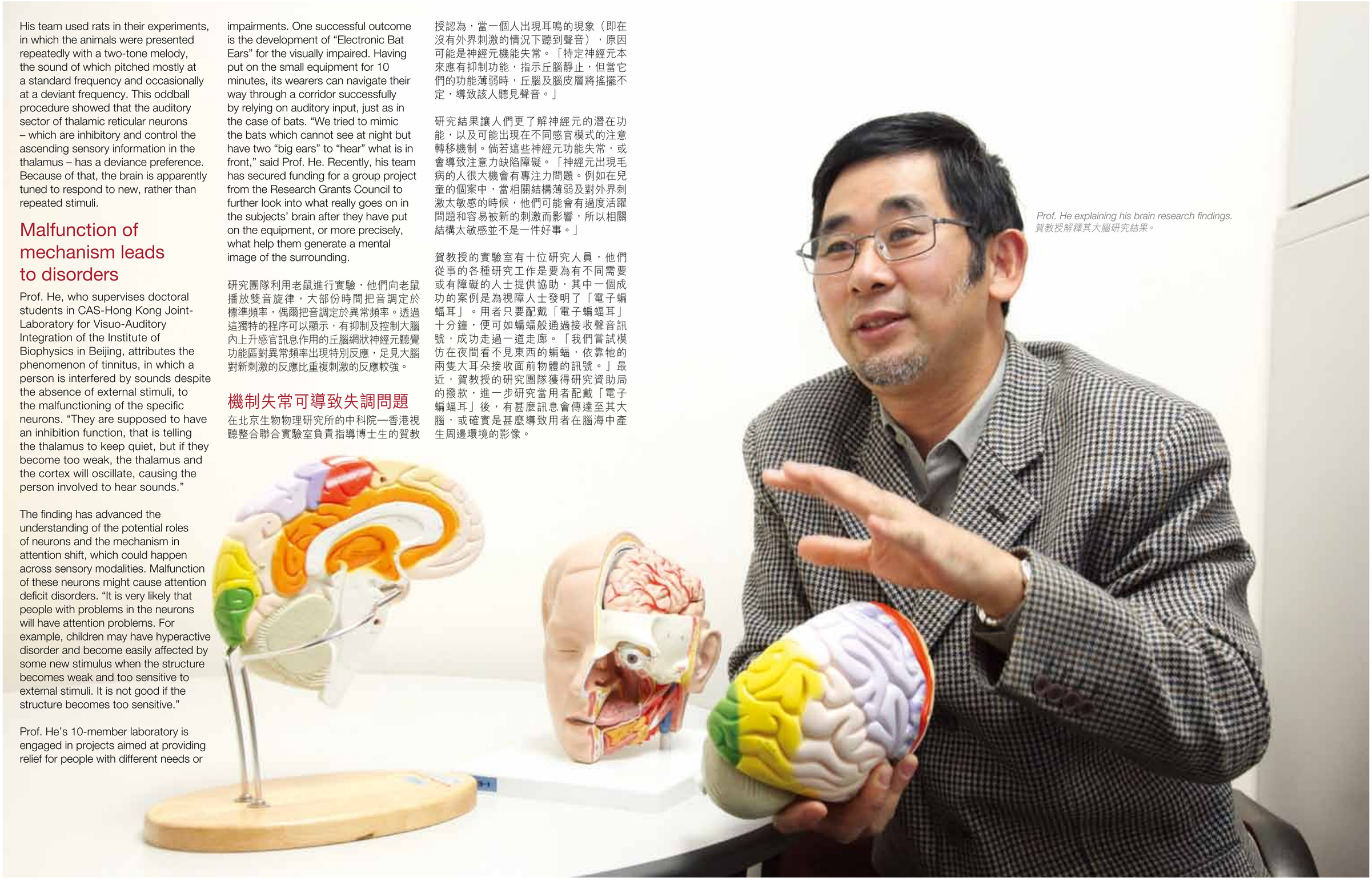
研究團隊利用老鼠進行實驗，他們向老鼠播放雙音旋律，大部份時間把音調定於標準頻率，偶爾把音調定於異常頻率。透過這獨特的程序可以顯示，有抑制及控制大腦內上升感官訊息作用的丘腦網狀神經元聽覺功能區對異常頻率出現特別反應，足見大腦對新刺激的反應比重複刺激的反應較強。

機制失常可導致失調問題

在北京生物物理研究所的中科院—香港視聽整合聯合實驗室負責指導博士生的賀教授認為，當一個人出現耳鳴的現象（即在沒有外界刺激的情況下聽到聲音），原因可能是神經元機能失常。「特定神經元本來應有抑制功能，指示丘腦靜止，但當它們的功能薄弱時，丘腦及腦皮層將搖擺不定，導致該人聽見聲音。」

研究結果讓人們更了解神經元的潛在功能，以及可能出現在不同感官模式的注意轉移機制。倘若這些神經元功能失常，或會導致注意力缺陷障礙。「神經元出現毛病的人很大機會有專注力問題。例如在兒童的個案中，當相關結構薄弱及對外界刺激太敏感的時候，他們可能會有過度活躍問題和容易被新的刺激而影響，所以相關結構太敏感並不是一件好事。」

賀教授的實驗室有十位研究人員，他們從事的各種研究工作是要為有不同需要或有障礙的人士提供協助，其中一個成功的案例是為視障人士發明了「電子蝙蝠耳」。用者只要配戴「電子蝙蝠耳」十分鐘，便可如蝙蝠般通過接收聲音訊號，成功走過一道走廊。「我們嘗試模仿在夜間看不見東西的蝙蝠，依靠牠的兩隻大耳朵接收面前物體的訊號。」最近，賀教授的研究團隊獲得研究資助局的撥款，進一步研究當用者配戴「電子蝙蝠耳」後，有甚麼訊息會傳達至其大腦，或確實是甚麼導致用者在腦海中產生周邊環境的影像。



Prof. He explaining his brain research findings.
賀教授解釋其大腦研究結果。

Commitment to neuroscience research

Since the 1990s, Prof. He, a native of Harbin on the Chinese mainland, has been drawn to the workings of the brain. His undergraduate and postgraduate education in electrical engineering at the Harbin Institute of Technology provided a good basis for his work. To facilitate their study, he and his team members, including his doctoral students and Prof. He Shigang of CAS Institute of Biophysics, manufactured electronic circuits to simulate the signal transmissions within the brain.

In the early 1990s, Prof. He Jufang went to Japan for a doctoral medical degree specializing in cardiology. But as vital as it is, the heart was not as stimulating as he had expected. Upon obtaining his PhD from the University of Tokushima, he changed his focus to neuroscience, an area greatly promoted by the Japanese Government then. He carried out post-doctoral work at RIKEN (Japan), and had also worked at HITACHI Ltd's Advanced Research Laboratory before joining PolyU in 1998.

Prof. He is well-driven by his fascination with the multifaceted brain functions. "If we can understand the brain better, we will be able to find different ways to help various patients, with less side effects," explained Prof. He. "Before we try to offer any help, we need to know how the system works, how we remember things, retrieve memory, experiences and the things we have learned. This is the first question we need to ask before we consider how to treat a patient. Understanding the mechanism is essential for getting the right medicine."

Prof. He showing his invention "Electronic Bat Ears" for people with visual impairments.
賀教授展示為視障人士而研發的「電子蝙蝠耳」。

Undoubtedly, both Prof. Han and Prof. He and their colleagues will continue to be challenged by plentiful investigation work on the brain, an area regarded by scientists to be the most difficult of all medical/life sciences. The dedicated efforts of PolyU researchers, hopefully, can pave the way for new discoveries of effective drugs that help change the lives of numerous sufferers of various brain diseases.

致力神經科學的研究

原籍中國內地哈爾濱的賀教授，自九十年代開始已醉心大腦的研究。他在哈爾濱工業大學取得電機工程學學士及碩士學位，這為他的研究工作奠定了良好的基礎。為方便進行研究，賀教授與研究團隊，包括在他指導下的博士生及中科院生物物理研究所的何士剛教授，自行製造電子電路來模擬大腦內的訊息傳送。

九十年代初期，賀教授在日本攻讀心臟科醫學博士學位，雖然這是一個很重要的學科，但賀教授對心臟的興趣沒有預期般大。於是，他在德島大學取得博士學位後，毅然轉向專攻神經科學的研究，這也是當時日本政府高度重視的科目。在一九九八年加入理大之前，賀教授曾在日本理化學研究所進行博士後研究，以及在日立有限公司高等研發實驗室工作。

賀教授對人腦的多方位功能非常嚮往，這一直是他研究工作背後的原動力。「如果我們對大腦多一點認識，就可以尋求不同的方法去幫助不同的病人，並且會有較少的副作用。」他解釋：「在為病人提供協助之前，我們必須明白大腦怎樣運作、怎樣記憶、怎樣從回憶、經歷、以及之前所學的知識中抽取資料，我們應該先理解這些問題，才考慮如何治療病人。要對症下藥，就必須了解大腦的運作。」

韓教授、賀教授和他們的團隊將繼續致力於極具挑戰性的大腦研究工作，這是一個被科學家視為最深奧的醫學或生命科學範疇。期望他們的努力可以有助日後發明有效藥物，為無數患腦部疾病人士的生命帶來轉機。

The research team of the CAS-Hong Kong Joint-Laboratory for Visuo-Auditory Integration
中科院—香港視聽整合聯合實驗室的研究團隊