Neuroscience News

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The Picower Institute
for learning and memory at MIT

Li-Huei Tsai, director of the Picower Institute for Learning and Memory. Photo / Betsy Cullen

FROM THE DIRECTOR

LI-HUEI TSAI

Neuroscience today is a field on the cusp of new discoveries. Only recently have the techniques and technologies of brain research reached a point where it is possible to explore the brain at every level of its complexity—from the molecular level to the cognitive system as a whole. The tools of the field have advanced in the past few years to a point where specific research questions can be addressed with unprecedented specificity. The Picower Institute for Learning and Memory is seizing new opportunities to focus our broad range of scientific talents on the targeted goal of unraveling the mechanisms that drive the characteristic human capacity to remember and learn.

The Institute features a highly collaborative, cross-disciplinary strategy that spawns exciting joint projects between its various labs. Many Picower faculty are also inventors of unique technologies and techniques that are redefining the practice of neuroscience. One of the Institute's longest collaborations is with Japan's Institute of Physical and Chemical Research, known as RIKEN, having created the RIKEN-MIT Neuroscience Research Center in 1998, and more recently the RIKEN-MIT Center for Neural Circuit Genetics in 2008. Under the directorship of my colleague Susumu Tonegawa, the RIKEN-MIT Center for Neural Circuit Genetics seeks to fully understand the brain mechanisms underlying specific cognitive phenomenon such as memory, emotion and decision-making. The Center investigates not only the properties of individual cells, cellular clusters, and brain systems, but also the functions generated by the neural circuits. This is vital to understanding the fundamental mechanisms operating in the healthy brain and how these mechanisms go astray under disease conditions.

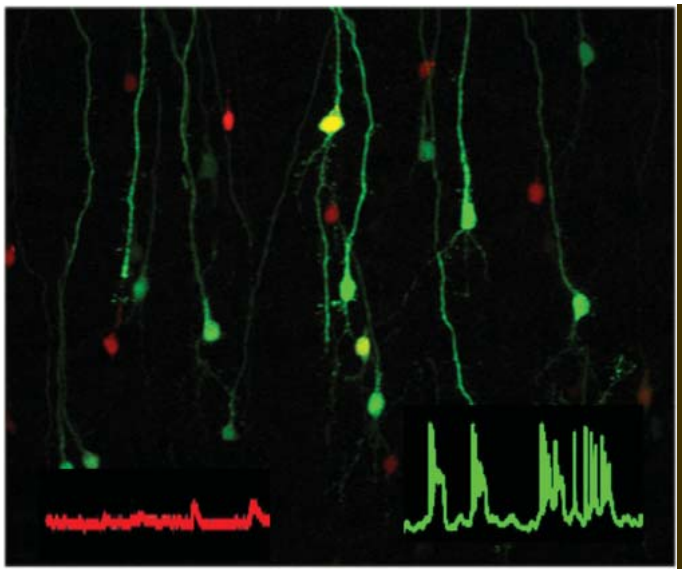
In more than ten years of working together, the RIKEN Brain Science Institute and the Picower Institute have created a strong, mutually beneficial relationship for collaborative research, building on the resources and strengths of both institutes. The ongoing RIKEN-MIT relationship will accelerate progress in the crucial scientific field of neural circuits.

The Picower Institute has another visionary collaboration with Boston University's Center of Excellence for Learning in Science, Education and Technology (CELEST). CELEST seeks to understand the fundamental processes that underlie human learning by studying dynamic interactions within and among brain regions. Led by my colleague Earl Miller of the Picower Institute, and co-directors Ennio Mingolla and Michael Hasselmo of Boston University, interdisciplinary research teams from four Boston-area universities study how the brain learns how to plan, explore, communicate and remember. CELEST also leverages its basic scientific research by broadening educational opportunities for students through curriculum development, and partnering with industry to transfer research breakthroughs to practical applications.

Li-Huei Tsai, Ph.D.

IN THIS ISSUE

Cover *Conceptual computer artwork of a human brain on a chessboard. This could represent the mental processes needed to tackle abstract problems such as playing chess. Image / Laguna Design / Science Photo Library*



Above *Neurons genetically rendered hyperactive (red) survive better than normal neurons (green). Traces at bottom of the image show the electrical activity of genetically-manipulated neurons (red trace) and normal neurons (green trace). Image / Carlos Lois*

'Noisiest' Neurons Persist in the Adult Brain, Research Finds

"Before, scientists believed the cells with the most accurate performance were selected and the others were rejected," said Picower Institute for Learning and Memory researcher Carlos Lois. "Our study shows that it doesn't matter what the cells are doing, as long as they are doing something, even if it is wrong. It's like musicians being chosen in an audition based not on how well they play, but how loudly."

Neuronal survival is a key component to the success of cell replacement therapies in the brain. Current therapies have hit a roadblock because the vast majority of grafted cells do not survive and do not integrate into adult brain circuits. "Our discovery of a survival-determining mechanism in new neurons is likely to have a significant influence on such treatments," said Lois, Assistant Professor of Neuroscience at the Picower Institute.

In addition, the observation that the "noisiest" neurons have a survival advantage helps explain the prevalence of epilepsy, in which some neurons become hyperactive and fire in an uncontrollable fashion. "Our work suggests that any perturbation that increases the activity of neurons will enhance the likelihood of their survival. Thus, during childhood, when many neurons are still being added to the brain, it is likely that neurons that become pathologically hyperactive will be preferentially selected for survival, and these abnormal neurons will be the trigger for epilepsy," Lois said.

To investigate whether activity levels – and the source and pattern of activity – are crucial in governing whether an individual new neuron survives or dies, the researchers used new technology to genetically enhance or dampen the electrical excitability of single adult-generated neurons. An important technological advance, the methods used in this study allow for single-cell genetic manipulation of electrical activity in living animals.

Investigating the molecular signals launched by neuronal activity will potentially lead to new drugs that bolster the survival of new neurons. These drugs could be used to increase the efficacy of treatments that depend on grafting stem cell-derived neurons into the adult brain to treat neurological diseases such as Parkinson's and Alzheimer's. ■

Magnesium Supplement Helps Boost Brainpower in Rats

Neuroscientists at MIT and Tsinghua University in Beijing show that increasing brain magnesium with a new compound enhanced learning abilities, working memory, and short- and long-term memory in rats. The dietary supplement also boosted older rats' ability to perform a variety of learning tests.

Magnesium, an essential element, is found in dark, leafy vegetables such as spinach and in some fruits. Those who get less than 400 milligrams daily are at risk for allergies, asthma, and heart disease, among other conditions. In 2004, Guosong Liu and colleagues at MIT discovered that magnesium might have a positive influence on learning and memory. They followed up by developing a new magnesium compound—magnesium-L-threonate (MgT) that is more effective than conventional oral supplements at boosting magnesium in the brain, and tested it on rats.

"We found that elevation of brain magnesium led to significant enhancement of spatial and associative memory in both young and aged rats," said Liu, now director of the Center for Learning and Memory at Tsinghua University. "If MgT is shown to be safe and effective in humans, these results may have a significant impact on public health." Liu is cofounder of Magceutics, a California-based company developing drugs for prevention and treatment of age-dependent memory decline and Alzheimer's disease.

"Half the population of the industrialized countries has a magnesium deficit, which increases with aging. If normal or even higher levels of magnesium can be maintained, we may be able to significantly slow age-related loss of cognitive function and perhaps prevent or treat diseases that affect cognitive function," Liu said.

To understand the molecular mechanisms underlying this MgT-induced memory enhancement, the researchers studied the changes induced in functional and structural properties of synapses. They found that in young and aged rats, MgT increased plasticity among synapses, the connections among neurons, and boosted the density of synapses in the hippocampus, a critical brain region for learning and memory.

Susumu Tonegawa at MIT's Picower Institute for Learning and Memory helped carry out the initial behavioral experiments that showed magnesium-boosted memory in aged rats. Min Zhou's laboratory at the University of Toronto helped demonstrate the enhancement of synaptic plasticity in magnesium-treated rats.

This study not only highlights the importance of diet with sufficient daily magnesium content for healthy individuals but also suggests the usefulness of magnesium-based treatments for aging-associated memory decline, Tonegawa said. Currently, clinical studies in Beijing are investigating the relationship between body magnesium

status and cognitive functions in aged human and Alzheimer's patients. ■

Gene helps regulate neuronal structure and functioning

In work that could lead to new insights into how neurons protect against neurodegeneration, researchers at MIT's Picower Institute for Learning and Memory report that a gene family known for its role in controlling cell proliferation and suppressing tumors is also essential in the brain to regulate neuronal structure and function.

Understanding how these processes normally work is key to dissecting what goes wrong in a host of neurological and psychiatric diseases. Defects in neuronal wiring have been implicated in developmental disorders such as autism and mental retardation. Working out the mechanisms by which neurons normally control their shapes can provide key insights into how this mechanism goes awry in disease states.

Using the common fruit fly Drosophila as a model, Picower Institute researcher J. Troy Littleton studies the connections that link together neurons within the brain. His lab elucidates how neurons form synaptic connections, how those connections work to transmit information and how the connections change during learning and memory.

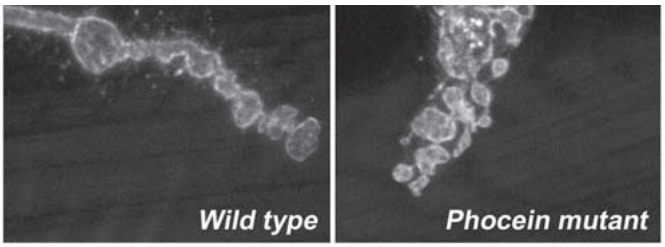
"What got us excited about this gene and its protein was the fact that members of this gene family had been previously shown to function as tumor suppressors," said Littleton, associate professor in the departments of Biology and Brain and Cognitive Sciences at MIT. "This work demonstrates an exciting tie-in of a known cancer-related gene family with a new role in neurodegeneration, potentially linking abnormal regulation of the cell cytoskeleton in pathologies as diverse as cancer and neurological diseases."

Understanding how a cell's internal scaffold, or cytoskeleton, mediates these diverse cell processes will shed new light into potential therapeutic approaches to potentially correct defects underlying certain disorders, he said.

The work revolves around a new member of the Mob protein family known for its role in cell division and as a cancer suppressor. Littleton and Joost Schulte, a postdoctoral associate in the Littleton laboratory, identified a member of this family, a protein called phocein/Mob4, as a key regulator of neuronal structure. When the protein is missing, neurons have abnormal branching patterns and connect improperly to target cells. These defects are tied to disruptions in the cell cytoskeleton. Mutants lacking the protein also have defects in the ability of neurons to transport cargo from the cell body to the synapse, which is critical for neurons to communicate and survive.

"We decided to characterize phocein because it is highly expressed in neurons and was found to control their elaborate branching structure, a key feature that makes neurons unique among other cells found in the body," Schulte said. Phocein is 80 percent identical between humans and fruit flies, suggesting it is likely to play a similar role across species in regulating neuronal structure.

Neurons extend a single long, thin axon and numerous shorter, thicker, branch-like dendrites. Information gathered and processed by the dendrites flows through the axons to synapses, through which neurons communicate within the brain.



Above *The abnormal synaptic morphology observed in phocein mutant synapses is shown. Image/Joost Schulte*

When Schulte knocked out the gene encoding phocein in fruit flies, their neurons become hyperbranched and had defective signaling. Given the role of the Mob family in regulating cell proliferation in cancer, the investigators suspect the protein has similar signaling partners in neurons, controlling the activation of key internal cell regulators.

The researchers stumbled across Phocein by screening the entire Drosophila genome to identify genes required for the formation of normal neural networks. "We were looking for genes that, when knocked out, cause defects in the growth, shape and structure of axons and dendrites," Littleton said.

By generating Drosophila phocein mutants, the researchers discovered that phocein has key roles in regulating neuronal shape and function within the nervous system.

The researchers are currently working on identifying partners that interact with phocein to better understand how it functions at the molecular level to interface with the underlying cytoskeleton. ■

In the News

Picower Institute faculty members were featured on national and international media outlets recently:

Elly Nedivi discussed her work on an actively regulated gene that is important for learning on the BBC Horizon show, "What Makes a Genius."

News of research findings by Susumu Tonegawa and former Picower researcher Guosong Liu on the fact that mice given extra doses of a new magnesium compound had better working memory, long-term memory and greater learning ability circled the globe. Venues included Fox News, the London Telegraph, The Times of India and WebMD.

The Boston Globe profiled Li-Huei Tsai, director of the Picower Institute, and her work on Alzheimer's disease.

The Science Daily feature, "'Noisiest' Neurons Persist in the Adult Brain, Research Finds" was about Carlos Lois's discovery that when it comes to new neurons in the adult brain, the squeakiest wheels get the grease.

Matt Wilson participated in a NOVA special, "What are dreams?" ■

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Above *Luckmini Liyanage, Boston Brain Bee Champion from Newton South High School and Rebecca R. Saxe, Ph.D., Boston Brain Bee Keynote Speaker. Photo / Alonso Nichols*

Picower hosts 2010 Boston regional Brain Bee

Students from more than a dozen Boston-area high schools competed Saturday, Feb. 27, in the 2010 Boston Regional Brain Bee at MIT's Picower Institute.

The event is one of more than 70 local Brain Bee competitions held all over the world to select competitors for the national and international Brain Bee championships held by the Society for Neuroscience (SfN).

Luckmini Liyanage from Newton South High School won first place; Yuan Ji from Belmont High School was in second place and third place went to Wenqi Feng from Newton South High School.

The Brain Bee is a live Q&A competition to see which students have the best knowledge of brain function and dysfunction, physiology and chemistry. Using "Brain Facts," a text developed by SfN, students are tested on paper to qualify for the oral competition limited to the top 10 students.

Winners from regional bees will go on to compete in the United States National Brain Bee March 15-21, during Brain Awareness Week.

Rebecca R. Saxe of the MIT Brain and Cognitive Sciences department gave the keynote address. Saxe studies theory of mind, the mechanism people use to infer and reason about another person's states of mind. ■

The 2009 BCS Holiday Party

The Picower Institute community, friends and family came together for food, entertainment and socializing at the 2009 holiday party, held Dec. 10 in the Building 46 atrium. The gathering was sponsored by the Picower Institute, the McGovern Institute for Brain Research and the MIT Brain and Cognitive Sciences Department. ■

Top Left *From left, Picower Institute Director Li-Huei Tsai, Mriganka Sur, Head of the Department of Brain and Cognitive Sciences, and Karuna Singh, postdoctoral fellow, Tsai Lab.* ***Top Right*** *From left, Earl K. Miller, Associate Director of the Picower Institute, and Matthew A. Wilson, Associate Head, Department of Brain and Cognitive Sciences and Picower faculty member.* ***Bottom Left*** *From left, Judith Korch, Assistant Director for Administration, Picower Institute, and Picower Institute Director Li-Huei Tsai.* ***Bottom Right*** *Assistant Professor of Neuroscience Weifeng Xu and daughter Angela. Photos / Matthew Cooney*

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MEET THE PICOWER INSTITUTE FACULTY

Top Row: Mark F. Bear Picower Professor of Neuroscience, Howard Hughes Medical Institute (HHMI) Investigator, Department of Brain and Cognitive Sciences; J. Troy Littleton Associate Professor, Departments of Biology and Brain and Cognitive Sciences; Carlos E. Lois Assistant Professor of Neuroscience, Departments of Brain and Cognitive Sciences and Biology; Earl K. Miller Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Associate Director of The Picower Institute for Learning and Memory; **Middle Row:** Elly Nedivi Associate Professor, Departments of Brain and Cognitive Sciences and Biology; Morgan H. Sheng Menicon Professor of Neuroscience, HHMI Investigator, Departments of Brain and Cognitive Sciences and Biology; Mriganka Sur Paul E. Newton Professor of Neuroscience, Head of the Department of Brain and Cognitive Sciences; Susumu Tonegawa Picower Professor of Biology and Neuroscience, RIKEN-MIT Investigator, HHMI Alumni Investigator, Departments of Biology and Brain and Cognitive Sciences; **Bottom Row:** Li-Huei Tsai Picower Professor of Neuroscience, HHMI Investigator, Department of Brain and Cognitive Sciences, Director of The Picower Institute for Learning and Memory; Matthew A. Wilson Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology, Associate Head, Department of Brain and Cognitive Sciences; Weifeng Xu Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences *Portraits/Betsy Cullen*

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