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

in this issue

Cover *This conceptual art of the human brain and its enigmatic waves illustrates our story on page 3 about a joint Picower Institute and McGovern Institute for Brain Research study in which MIT researchers induced gamma waves in mice with new laser technology. Image / Pasieka, Science Photo Library*

from the director
li-huei tsai

It is with great humility that I assume the position of director of the Picower Institute for Learning and Memory. Under the stewardship of founder Susumu Tonegawa and Mark Bear, who stepped down July 1 after more than two years as director, the Picower Institute has made contributions at the forefront of understanding the mechanisms underlying memory formation at the molecular, cellular, circuit and systems levels and has established itself as the leading institute in neuroscience research.

The Picower Institute was founded in 1994 with the goal of providing a world-class environment for research and education in neuroscience, focusing on learning and memory. The institute aims to unlock the mechanisms of learning and memory at the molecular, cellular, circuit and systems levels—mechanisms that are key to understanding the pathophysiology of neurological disorders affecting cognition and exploring new approaches for therapeutic intervention.

One of my goals is to continue to foster collaborations with colleagues both within and outside the Picower Institute and to promote relationships between the MIT neuroscience community and the Stanley Center for Psychiatric Research at the Broad Institute.

As director, my responsibility will be to continue the long-term mission of the institute in pursuing the understanding of higher cognitive functions in a collaborative and intellectual atmosphere. In the short term, my goal is to recruit the brightest junior faculty to further enrich the scientific environment of the Picower Institute and the MIT neuroscience community.

I am truly honored by the trust that has been placed in me to lead the Picower Institute and I look forward to working with each of the faculty and staff to address the challenges we now face. Working together, I am confident that we can make our Institute an even better home for research and education.

(A brief biography of Li-Huei Tsai is featured on page 5.)

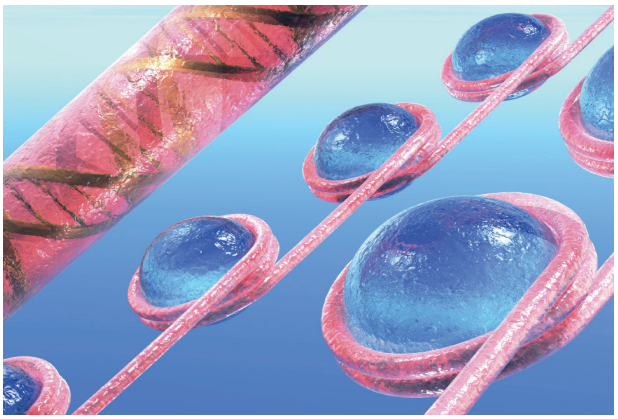
Li-Huei Tsai, Ph.D.

in the news

Several findings from Picower Institute laboratories were featured prominently in the media recently. Work by study lead author Li-Huei Tsai, Picower Professor of Neuroscience, showed that a key player in "wrapping" DNA is an enzyme called histone deacetylase-2 (HDAC2). HDAC2's job in the cell is to control how tightly chromosomal DNA wraps around protein spools called histones. (See story on page 3.) The story ran in Forbes, US News and World Report, the BBC and more than 50 other media outlets in May.

Work by MIT affiliate Mariko Hayashi investigating a sometimes-faulty protein's role in brain links appeared on the site PhysOrg.com. That story highlighted a Picower study that sheds light on how a protein implicated in cognitive disorders maintains and regulates brain cell structures that are key to learning and memory.

A joint study between the McGovern Institute for Brain Research and the Picower Institute announced that scientists have discovered a way to induce gamma waves by shining laser light directly onto the brains of mice. High-frequency brain waves known as gamma oscillations are thought to be crucial for consciousness, attention, learning and memory. (See story page 3.) This work was featured by several news outlets. ■



Above *In this computer artwork, strands of DNA shown in pink are coiled around histone cores, shown to form the less-condensed, beads-on-a-string form of chromatin. Work by Li-Huei Tsai centers around HDAC inhibitors that open up chromatin to allow better transcription and expression of genes. Image/Laguna Design, Science Photo Library.*

team identifies gene key to reversal of alzheimer's-like symptoms

A team led by researchers at MIT's Picower Institute for Learning and Memory has now pinpointed the exact gene responsible for a 2007 breakthrough in which mice with symptoms of Alzheimer's disease regained long-term memories and the ability to learn.

In the latest development, reported in Nature, Li-Huei Tsai, Picower Professor of Neuroscience, and colleagues found that drugs that work on the gene HDAC2 reverse the effects of Alzheimer's and boost cognitive function in mice.

"This gene and its protein are promising targets for treating memory impairment," Tsai said. "HDAC2 regulates the expression of a plethora of genes implicated in plasticity — the brain's ability to change in response to experience — and memory formation.

"It brings about long-lasting changes in how other genes are expressed, which is probably necessary to increase numbers of synapses and restructure neural circuits, thereby enhancing memory," she said.

The researchers treated mice with Alzheimer's-like symptoms using histone deacetylase (HDAC) inhibitors. HDACs are a family of 11 enzymes that seem to act as master regulators of gene expression. Drugs that inhibit HDACs are in experimental stages and are not available by prescription for use for Alzheimer's.

"Harnessing the therapeutic potential of HDAC inhibitors requires knowledge of the specific HDAC family member or members linked to cognitive enhancement," Tsai said. "We have now identified HDAC2 as the most likely target of the HDAC inhibitors that facilitate synaptic plasticity and memory formation.

"This will help elucidate the mechanisms by which chromatin remodeling regulates memory," she said. It also will shed light on the role of epigenetic regulation, through which gene expression is indirectly influenced, in physiological and pathological conditions in the central nervous system.

"Furthermore, this finding will lead to the development of more selective HDAC inhibitors for memory enhancement," she said. "This is exciting because more potent and safe drugs can be developed to treat Alzheimer's and other cognition diseases by targeting this HDAC specifically," said Tsai, who is also a Howard Hughes Medical Institute investigator. Several HDAC inhibitors are currently in clinical trials as novel anticancer agents and may enter the pipeline for other diseases in the coming two to four years. Researchers have had promising results with HDAC inhibitors in mouse models of Huntington's disease.

Proteins called histones act as spools around which DNA winds, forming a structure in the cell nucleus known as chromatin. Histones are modified in various ways, including through a process called acetylation, which in turn modifies chromatin shape and structure. (Inhibiting deacetylation with HDAC inhibitors leads to increased acetylation.)

Certain HDAC inhibitors open up chromatin. This allows transcription and expression of genes in what had been a too tightly packaged chromatin structure in which certain genes do not get transcribed.

There has been exponential growth in HDAC research over the past decade. HDAC inhibitors are currently being tested in preclinical studies to treat Huntington's disease. Some HDAC inhibitors are on the market to treat certain forms of cancer. They may help chemotherapy drugs better reach their targets by opening up chromatin and exposing DNA. "To our knowledge, HDAC inhibitors have not been used to treat Alzheimer's disease or dementia," Tsai said. "But now that we know that inhibiting HDAC2 has the potential to boost synaptic plasticity, synapse formation and memory formation, in the next step, we will develop new HDAC2-selective inhibitors and test their function for human diseases associated with memory impairment to treat neurodegenerative diseases." ■

using lasers, researchers achieve a first: induced gamma waves in mice

Scientists have studied high-frequency brain waves, known as gamma oscillations, for more than 50 years, believing them crucial to consciousness, attention, learning and memory. Now, for the first time, MIT researchers and colleagues have found a way to induce these waves by shining laser light directly onto the brains of mice.

The work takes advantage of a newly developed technology known as optogenetics, which combines genetic engineering with light to manipulate the activity of individual nerve cells. The research helps explain how the brain produces gamma waves and provides new evidence of the role they play in regulating brain functions — insights that could someday lead to new treatments for a range of brain-related disorders.

"Gamma waves are known to be [disrupted] in people with schizophrenia and other psychiatric and neurological diseases," says Li-Huei Tsai, Picower Professor of Neuroscience and a Howard Hughes Medical Institute investigator. "This new tool will give us a great chance to probe the function of these circuits."

Tsai co-authored a paper about the work that appeared in Nature.

Gamma oscillations reflect the synchronous activity of large interconnected networks of neurons, firing together at frequencies ranging from 20 to 80 cycles per second. "These oscillations are thought to be controlled by a specific class of inhibitory cells known as fast-spiking interneurons," says Jessica Cardin, co-lead author on the study and a postdoctoral fellow at MIT's McGovern Institute for Brain Research. "But until now, a direct test of this idea was not possible."

To determine which neurons are responsible for driving the oscillations, the researchers used a protein called channelrhodopsin-2 (ChR2), which can sensitize neurons to light. "By combining several genetic tricks, we were able to express ChR2 in different classes of neurons, allowing us to manipulate their activity with precise timing via a laser and an optical fiber over the brain," explains co-lead author Marie Carlén, a postdoctoral fellow at the Picower Institute.

The trick for inducing gamma waves was the selective activation of the "fast-spiking" interneurons, named for their characteristic pattern of electrical activity. When these cells were driven with high frequency laser pulses, the illuminated region of cortex started to produce gamma oscillations. "We've shown for the first time that it is possible to induce a specific brain state by activating a specific cell type" says co-author Christopher Moore, associate professor of neuroscience and an investigator in the McGovern Institute. In contrast, no gamma oscillations were induced when the fast-spiking interneurons were activated at low frequencies, or when a different class of neurons was activated.

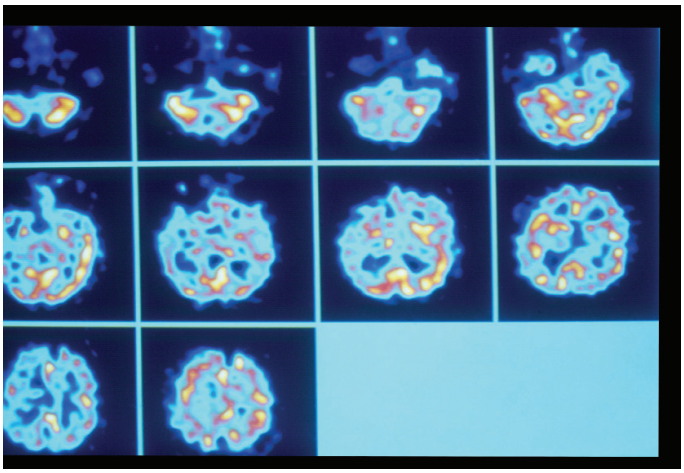
The authors further showed that these brain rhythms regulate the processing of sensory signals. They found that the brain's response to a tactile stimulus was greater or smaller depending on exactly where the stimulus occurred within the oscillation cycle. "It supports the idea that these synchronous oscillations are important for controlling how we perceive stimuli," says Moore. "Gamma rhythms might serve to make a sound louder, or a visual input brighter, all based on how these patterns regulate brain circuits."

Because this new approach required a merger of expertise from neuroscience and molecular genetics, three different laboratories contributed to its completion. In addition to Tsai, Moore and Carlén of MIT, co-authors include Jessica Cardin, research affiliate at the McGovern Institute and the University of Pennsylvania, and Karl Deisseroth and Feng Zhang at Stanford University. Other co-authors were Konstantinos Meletis, a postdoctoral fellow at the Picower Institute, and Ulf Knoblich, a graduate student in MIT's Department of Brain and Cognitive Sciences. ■

blocked enzyme reverses schizpohrenia-like symptoms in mice

Researchers at MIT's Picower Institute for Learning and Memory have found that inhibiting a key brain enzyme in mice reversed schizophrenia-like symptoms.

The finding, reported in Cell, identified how a particular gene controls this brain enzyme. Better understanding of the relationship could lead to new drug treatments for schizophrenia, the severe brain disorder that affects about 1 percent of the



Above *This image depicts a series of positron emission tomography (PET) scans of the brain of an hallucinating patient suffering from schizophrenia. Schizophrenia ("split personality") is characterised by delusions, hallucinations and depression. Photo/Tim Beddow/Science Photo Library*

population and is characterized by hallucinations, delusions, poor social and emotional functioning and disorganized thoughts.

The Picower research focused on a gene known as DISC1 (short for "disrupted in schizophrenia 1"), which was first identified in the 1990s by researchers studying the genetic makeup of a large Scottish family with mental and behavioral disorders. DISC1 has since been shown to help brain neuronal cells migrate to their correct positions and to help new neurons grow in the developing brain, but its role was not well understood.

Now, Li-Huei Tsai, Picower Professor of Neuroscience in MIT's Department of Brain and Cognitive Sciences, and colleagues have shown for the first time that DISC1 directly inhibits the activity of a brain enzyme called glycogen synthase kinase 3 beta, also known as GSK3B.

Lithium chloride, the mood-stabilizing drug often prescribed for schizophrenia and bipolar disorder, also acts on GSK3B.

"This work for the first time provides a detailed explanation of how DISC1 functions normally in our brains," said Tsai, a Howard Hughes Medical Institute investigator and director of the neurobiology program of the Stanley Center for Psychiatric Research at the Broad Institute.

"With this new knowledge of the DISC1-GSK3B interaction, one of the goals is to develop new drugs targeting schizophrenia, providing some hope that this devastating disease will be treated more effectively in the near future," she said.

Working with mice, Tsai and colleagues found that DISC1 regulates the growth of neural stem cells in both developing and adult brains. "During brain development, a fine-tuned mechanism regulates when neural stem cells divide and replenish their own population and when they turn into newborn neurons that will mature and grow appropriate connections with other neurons," Tsai said. ■

Donor profile - Support for the Miller Lab

Above *Linda and Richard Hardy . Photo / John Currier*

In July 2008, MIT alumnus Richard Hardy's daughter happened to tell him about an article in the The New Yorker that touched on the work of Earl K. Miller, Picower Professor of Neuroscience. The story said that Miller was able to show that the prefrontal cortex "wasn't simply an aggregator of information, but rather it was more like a conductor, waving its baton and directing the players."

Hardy, an engineer with a strong interest in neuroscience, had written a book called "The Rational Decision Brain" in 2002, and was intrigued by Miller's approach. After more investigation, Hardy decided that the Miller lab was conducting critical work "in terms of enabling people to understand and deal with their lives and economic and political systems. When we understand how consciousness works, we will understand how people think and how they make decisions."

Hardy and his wife, Linda, recently made a generous contribution in support of Miller's research related to the neural basis of working, or short-term memory, which is tightly linked to consciousness.

After he read the New Yorker piece called 'The Eureka Hunt," Hardy sent a copy of his book to Miller. It turns out that the Hardy family had been reviewing consciousness research at various institutions and discovered what they were specifically looking for – fundamental research focused on the sequential aspects to conscious thought patterns. Coincidentally, this research was going on MIT, Hardy's alma mater.

Hardy graduated from MIT in 1958 with a bachelor's in aeronautics and astronautics and also a bachelor's in mechanical engineering. In 1959, he earned a master's in aeronautics and astronautics. Later that year, he joined Boeing, where he worked for the next 37 years. After two years in retirement, he launched Hardy Engineering and Manufacturing Co., an aerospace firm in Auburn, Wash.

Linda, his wife of 50 years, is a graduate of Skidmore College, with a master's in early childhood education from the University of Washington and a certificate from the Saint Nicholas Training Center for the Montessori Method of London. She ran a Montessori School for 39 years, dedicating her career to the education of future generations.

The Hardys support a number of MIT programs, including the Department of Aeronautics and Astronautics and MIT athletics. Their eldest granddaughter, Gina Fridley, graduated from MIT on June 5, 2009, and her sister, Lila Fridley, is a member of the Class of 2013.

The Hardy gift fills a critical funding gap in the Miller lab, replacing support formerly provided by the Picower Institute Innovation Fund that was halted when The Picower Foundation closed. ■

Above *Linda and Richard Hardy . Photo / John Currier*

Picower community thanks former director mark f. bear

Picower Institute researchers and graduate students attended the 2nd annual Dana and Betty Fisher Retreat of the Picower Institute. Held at the Sea Crest Oceanfront Resort and Conference Center in North Falmouth, Mass., on June 3-4, 12 posters were presented by the Littleton, Sur, Tsai, Miller, Tonegawa and Bear laboratories. Representatives of the Bear, Nedivi, Xu and Tonegawa laboratories also presented slide show overviews of current work.

Neurobiologist Jeff Lichtman of Harvard University gave the keynote speech, "Plumbing the Connections," on June 3. When Italian physician and scientist Lichtman is creating what he calls a "Technicolor golgi"— a colorful map of tiny, long thin, tangled fibers representing each type of neuron in the human brain and how they interconnect. Even though this wiring diagram looks hopelessly complex, Lichtman's goal is to elucidate the rhyme and reason behind it.

He believes that, like mapping the human genome, mapping brain circuitry will hold the key to deeper understanding of the human brain. Unlike lower organisms, he said, "genes did not determine these maps." Instead, experience shapes the brain to such an extent that we have moved far beyond our genetic blueprint for basic life functions, he said. ■

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for learning and memory at MIT

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Top Row: Mark F. Bear Picower Professor of Neuroscience, Howard Hughes Medical Institute (HHMI) Investigator, Department of Brain and Cognitive Sciences; Yasunori Hayashi Assistant Professor of Neurobiology, RIKEN 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; **Middle Row:** Earl K. Miller Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Associate Director of The Picower Institute for Learning and Memory; 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; **Bottom Row:** Susumu Tonegawa Picower Professor of Biology and Neuroscience, RIKEN-MIT Investigator, HHMI Alumni Investigator, Departments of Biology and Brain and Cognitive Sciences; 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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