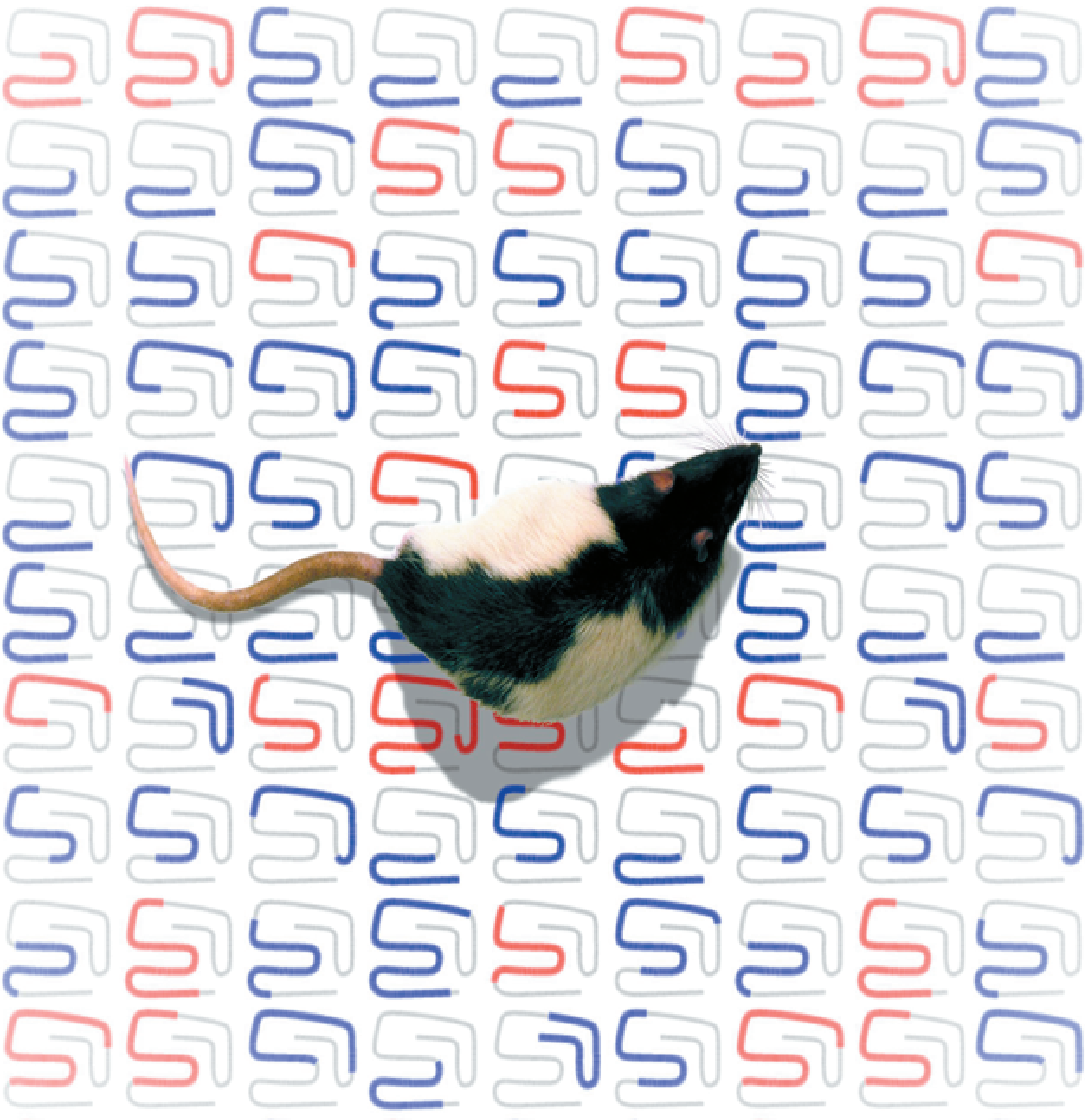


Neuroscience News

Fall 2009
Volume 4, Number 2

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

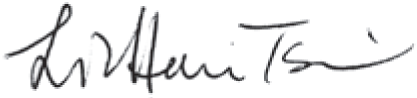
LI-HUEI TSAI

As I look back over fiscal year 2009, I see a year filled with excitement about the direction of Picower Institute research and the promising new results generated by our community of faculty and researchers. I am proud to communicate that in the past year Picower Institute faculty published 16 articles in hallmark science journals (Science, Neuron, Cell, Nature, and Nature Neuroscience) and 46 peer-reviewed publications overall. I also see a time of great economic challenge as the true scope of the worldwide recession became apparent. National economic woes hit the Picower Institute close to home when we learned in late December 2008 that the Picower Foundation, the 71st largest in the country, would be forced to close.

While the majority of our external research funding at the Picower Institute continues to come from the National Institutes of Health and the Howard Hughes Medical Institute, the loss of the Picower Foundation left the Picower Institute Innovation Fund in jeopardy. Launched by my predecessor, Mark Bear, the Fund was created to allow faculty to pursue innovative high-risk, high-reward research projects. Like the Picower Institute, many organizations are seeking increased government funding and possess an urgent and growing need for financial support from the private sector. I am pleased to announce that a generous commitment from MIT alumnus Richard Hardy and his wife, Linda, will fill a critical research funding gap for Earl Miller's laboratory. (See story on page 5.)

As we look toward the future, there are other opportunities for sustaining our progress and ensuring growth at the Picower Institute. As I stated in our last newsletter, recruitment of extraordinary talent is a high priority to fulfill our long-term vision. Intense competition for the top neuroscientists continues to place an emphasis on guaranteed laboratory space, start-up costs, and professorships. With the vitality and excitement of my current colleagues, I hope to secure the necessary support to add key faculty members who will enrich our remarkable contributions in the field.

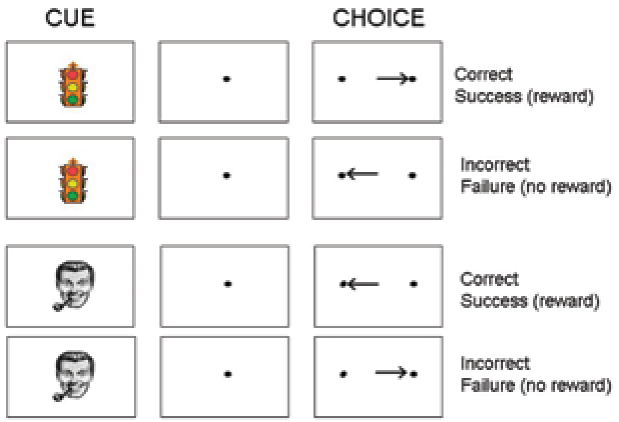
Major progress is being made every day toward understanding the brain, our most critical and mysterious organ. Neuroscience is one of the last frontiers of human biology, with 90 percent of what we have learned about the brain having been elucidated in the past 15 years. We still have a long way to go toward fully understanding brain function, but we envision a future in which neurological diseases and disorders are significantly ameliorated by ongoing cutting-edge work at the Picower Institute.



Li-Huei Tsai, Ph.D.

IN THIS ISSUE

Cover *Researchers at MIT's Picower Institute for Learning and Memory have found that rats use a mental instant replay of their actions to help them decide what to do next, shedding new light on how animals and humans learn and remember. See story on page 3. Photo illustration / Fabian Kloosterman / Wilson laboratory*



Above *Given different images as cues, monkeys were trained to look right or left for rewards. Picower Institute neuroscientists found that neurons responded differently following correct and incorrect responses, with correct responses setting up the brain for additional successes. Image / Earl Miller laboratory*

Why we learn more from our successes than our failures

If you've ever felt doomed to repeat your mistakes, researchers may have explained why: brain cells may only learn from experience when we do something right and not when we fail.

In a recent issue of the journal Neuron, Earl K. Miller, Picower Professor of Neuroscience, and MIT colleagues, Mark Histed and Anitha Pasupathy, have created for the first time a unique snapshot of the learning process that shows how single cells change their responses in real time as a result of information about what is the right action and what is the wrong one.

"We have shown that brain cells keep track of whether recent behaviors were successful or not," Miller said. Furthermore, when a behavior was successful, cells became more finely tuned to what the animal was learning. After a failure, there was little or no change in the brain — nor was there any improvement in behavior.

The study sheds light on the neural mechanisms linking environmental feedback to neural plasticity — the brain's ability to change in response to experience. It has implications for understanding how we learn, and understanding and treating learning disorders.

Monkeys were given the task of looking at two alternating images on a computer screen. For one picture, the animal was rewarded when it shifted its gaze to the right; for another picture it was supposed to look left. The monkeys used trial and error to figure out which images cued which movements.

The researchers found that whether the animals' answers were right or wrong, signals within certain parts of their brains "resonated" with the repercussions of their answers for several seconds. The neural activity following a correct answer and a reward helped the monkeys do better on the trial that popped up a few seconds later.

"If the monkey just got a correct answer, a signal lingered in its brain that said, 'You did the right thing.' Right after a correct answer, neurons processed information more sharply and effectively, and the monkey was more likely to get the next answer correct as well," Miller said, "But after an error there was no improvement. In other words, only after successes, not failures, did brain processing and the monkeys' behavior improve."

Response selectivity was stronger on a given trial if the previous trial had been rewarded and weaker if the previous trial was an error. This occurred whether the animal was just learning the association or was already good at it.

After a correct response, the electrical impulses coming from neurons in each of the brain areas was more robust and conveyed more information. "The signal-to-noise ratio improved in both brain regions," Miller said. "The heightened response led to them being more likely to get the next trial correct, too. This explains on a neural level why we seem to learn more from our successes than our failures."

In addition to Miller, authors include former MIT graduate student Mark H. Histed, now a postdoctoral fellow at Harvard Medical School, and former postdoctoral fellow Anitha Pasupathy, now an assistant professor at the University of Washington. ■

Rats' mental 'instant replay' drives next moves

Rats use a mental instant replay of their actions to help them decide what to do next, shedding new light on how animals and humans learn and remember. The work appeared in the journal Neuron.

"By understanding how thoughts and memories are structured, we can gain insight into how they might be disrupted in diseases and disorders of memory and thought such as Alzheimer's and schizophrenia," said study author Matthew A. Wilson, the Sherman Fairchild Professor of Neuroscience at the Picower Institute. "This understanding may lead to new methods of diagnosis and treatment."

Wilson's previous work has shown that after the animals run a maze, their brains "replay" during sleep the sequence of events they experienced while awake. Researchers believe this process is key to sleep-reinforced memory consolidation in both animals and humans. The latest study shows that these sequences also occur when the animals are awake and may help them decide what to do next.

When a rat moves through a maze, certain neurons called "place cells," which respond to the animal's physical environment, fire in patterns and sequences unique to different locations. By looking at the patterns of firing cells, researchers can tell which part of the maze the animal is running.

While the rat is awake but standing still in the maze, its neurons fire in the same pattern of activity that occurred while it was running. The mental replay of sequences of the animals' experience occurs in both forward and reverse time order.

"This may be the rat equivalent of 'thinking,'" Wilson said. "This thinking process looks very much like the reactivation of memory that we see during non-REM dream states, consisting of bursts of time-compressed memory sequences lasting a fraction of a second.

"So, thinking and dreaming may share the same memory reactivation mechanisms," he said.

The team's results show that long experiences, which in reality could have taken tens of seconds or minutes, are replayed in only a fraction of a second. To do this, the brain links together smaller pieces to construct the memory of the long experience.

The researchers speculated that this strategy could help different areas of the brain share information — and deal with multiple memories that may share content — in a flexible and efficient way. "These results suggest that extended replay is composed of chains of shorter subsequences, which may reflect a strategy for the storage and flexible expression of memories of prolonged experience," Wilson said.

Moreover, by comparing the content of the replay with the rat's physical location on the track and his actual behavior immediately before and after the replay event the researchers could tell the rat was not just thinking about his most recent experience, but also about other options, such as: "What if I turned around and went back the way I came?" or "How would I get here if my starting point is at a distant location?"

This suggests that the same brain mechanisms come into play to remember the past and consider future actions, reinforcing recent work by neuroscientists outside of MIT who determined that in humans, cognitive processes related to episodic recall and evaluation of future events overlap to a high degree.

The MIT researchers plan to further explore the link between awake replay and cognition in animals engaged in more cognitively demanding tasks such as those involving multiple choices, where the rat has to make a decision ("do I go left or right?") based on a prior learned rule.

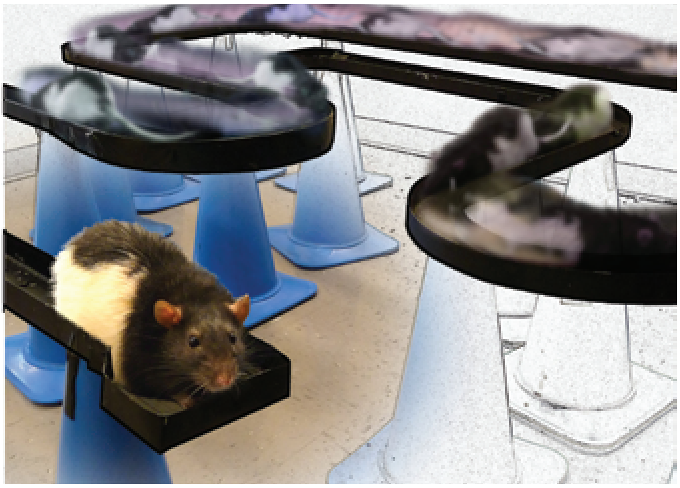
In addition to Wilson, the study was led jointly by Kloosterman and MIT brain and cognitive sciences graduate student Thomas J. Davidson. ■

The mind's eye scans like a spotlight

You're meeting a friend in a crowded cafeteria. Do your eyes scan the room like a roving spotlight, moving from face to face, or do you take in the whole scene, hoping that your friend's face will pop out at you? And what, for that matter, determines how fast you can scan the room?

Researchers at MIT's Picower Institute for Learning and Memory say you are more likely to scan the room, jumping from face to face as you search for your friend. In addition, the timing of these jumps appears to be determined by waves of activity in the brain that act as a clock. The study, which appeared in the journal Neuron, sheds new light on a long-standing debate among neuroscientists over how the visual system picks out an object of interest in a complex scene.

In the study, monkeys were given the task of searching for one particular tilted, colored bar among a field of bars on a computer screen. By monitoring the activity of neurons in three of the animals' brain regions, researchers found that the monkeys



Above *As a rat pauses during exploration of a long track, firing sequences corresponding to recent experiences are replayed at high speed in the hippocampus. Image/Fabian Kloosterman and Greg Hale*

spontaneously shifted their attention in a sequence, like a moving spotlight that jumped from location to location.

What's more, the study showed that brain waves act as a kind of built-in clock that provides a framework for shifting attention from one location to the next. The work could have implications for understanding or treating attention deficit disorder or even potentially speeding up the rate of cognition in the brain.

"For many years, neuroscientists have been debating competing theories on whether humans and animals spontaneously search elements of a visual scene in a serial or parallel manner," said lead author Earl K. Miller, Picower Professor of Neuroscience. "Ours is the first study based on direct evidence of neurophysiological activity."

Activity in the brain comes and goes in waves, cycling between high and low activity states. Researchers have been recording brain waves for more than 100 years and although they think they play roles in working memory, decision-making and communication among brain regions, no one is sure of their exact role in brain function. This work suggests a new role for brain waves — one in which they are directly involved in the brain's processing.

Picower Institute postdoctoral associate and co-author Timothy J. Buschman found that the spotlight of the mind's eye shifted focus at 25 times a second and that this process of switching was regulated by brain waves. "This is one of the first examples of how brain waves play a specific role in cognitive computations," Buschman said.

"Attention regulates the flood of sensory information pouring into the brain into a manageable stream. In particular, a lot of different areas of the brain are involved in vision. If they all competed at once, it would be chaos," Miller said. "Brain waves may provide the clock that tells the brain when to shift its attention from one stimulus to another. Oscillating brain waves may provide a way for several regions across the brain to be on the same page at the same time — very similar to the way computers use an internal clock to synchronize the many different components inside." ■

Above *Director Li-Huei Tsai and former director Mark F. Bear. Photo/Derek Buhl*

Picower community thanks former director Mark F. Bear

Outgoing Picower Institute director Mark F. Bear congratulates Li-Huei Tsai on becoming the Institute's third director at an event August 21 in the Picower Reading Terrace. Both researchers are Picower Professors of Neuroscience and Howard Hughes Medical Institute investigators. At the event, Picower faculty and staff held an informal presentation thanking Bear for his hard work, dedication and contributions as director.

Bear 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. ■

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 featured the work of Earl K. Miller, Picower Professor of Neuroscience. The story said 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 laboratory 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, Washington.

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 laboratory, replacing support formerly provided by the Picower Institute Innovation Fund that was halted when The Picower Foundation closed. ■

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Massachusetts Institute of Technology
77 Massachusetts Avenue Building 46 Room 1303
Cambridge, MA 02139-4307

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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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Ms. Martha J. Ruest
Director of Development
Tel: 617-253-5563
Email: mruest@mit.edu

CONTACT THE PICOWER INSTITUTE

MIT
The Picower Institute for Learning and Memory
77 Massachusetts Avenue
Building 46 Room 1303
Cambridge, MA 02139-4307

Tel 617-324-0305
web.mit.edu/picower