Memory and its Meaning

25 Years of Picower Institute Research

Neuroscience News

MIT FALL 2019

THE PICOWER INSTITUTE FOR LEARNING AND MEMORY

DIRECTOR'S **MESSAGE**

Dear Friends,

With a theme like "memory" it's natural to think about the past, the future and the work we do to ensure that as time goes by, we make progress.

Our cover story (see p. 7) illustrates many ways we have made progress in the enterprise of memory research that launched the Institute 25 years ago. We started with a generous and pivotal grant from the Sherman Fairchild Foundation and then in 2002 became incredibly fortunate to gain the transformative and sustaining support of Barbara and Jeffry Picower. What Picower Institute scientists have found about the brain's memory systems has often been unexpected and astonishing. And as you'll also see in the pages that follow, our desire to make further inroads both in fundamental discovery and also in translational work to address disease is as strong as ever.

While memory research is integral to our very name, it is not all that we do. From early on Picower Institute research has also investigated the fundamental sub-cellular mechanisms that allow the brain to learn and adapt with experience (a phenomenon called "plasticity"). Our research also encompasses related brain functions – like cognition, consciousness, perception and behavior – that also define us in health and sickness. In these areas, too, we have been able to help the neuroscience field make encouraging progress. We'll discuss some of the state of the art in October at our Fall Symposium, "Neural Mechanisms of Memory and Cognition" (p. 11).

I believe such advancement will surely continue. I'm encouraged, for example, by our up and coming talent. This summer, for instance, Kwanghun Chung earned a top federal honor: the Presidential Early Career Award for Scientists and Engineers (p. 5). We are also excited and grateful that the JPB Foundation has renewed and extended two fellowship programs that support and nurture many of our most promising postdocs (p. 6).

Even as we remember the past, we continue to work for the future.

LI-HUEI TSAI, DIRECTOR
The Picower Institute for Learning and Memory

How Neurons Make Synapses Keepers

Neurons frequently test out new potential circuit connections through transient contacts, but only a fraction of fledging junctions, called synapses, are selected to become permanent.

The major criterion for excitatory synapse selection is based on how well they engage in response to experience-driven neural activity. How such selection is implemented at the molecular level has been unclear. In a new study, MIT neuroscientists identify the gene and protein, CPG15, that allows experience to tap a synapse as a keeper.

In *Cell Reports* the Picower Institute team used multi-spectral, high-resolution two-photon microscopy to literally watch potential synapses come and go in the visual cortex of mice – both in the light, or normal visual experience, and in the darkness, where there is no visual input. By comparing observations made in normal mice and ones engineered to lack CPG15, they showed that the protein is required in order for visual experience to facilitate the transition of nascent excitatory synapses to permanence.

Mice engineered to lack CPG15 only exhibit one behavioral deficiency: They learn much more slowly than normal mice, said senior author Elly Nedivi, William R. (1964) & Linda R. Young Professor of Neuroscience. The new study suggests that's because without CPG15, they must rely on circuits where synapses simply happened to take hold, rather than on a circuit architecture that has been refined by experience for optimal efficiency.

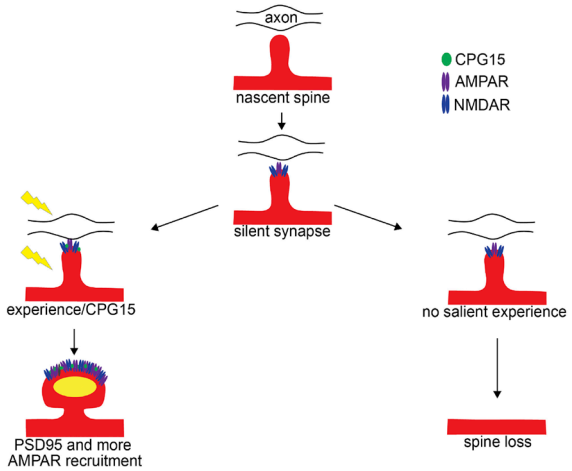
"Learning and memory are really specific manifestations of our brain's ability in general to constantly adapt and change in response to our environment," Nedivi said. "It's not that the circuits aren't there in mice lacking CPG15, they just don't have that feature, which is really important, of being optimized through use."

Led by former MIT postdoc Jaichandar Subramanian, the paper demonstrates novel labeling and imaging technologies to allow tracking key events in synapse formation with unprecedented spatial and temporal resolution. The study resolved the emergence of "dendritic spines," which are the structural protrusions on which excitatory synapses are formed, and the recruitment of the synaptic scaffold, PSD95, that signals that a synapse is there to stay.

They hypothesized that CPG15 carries the message of experience to bring PSD95 to the synapse. To test that, the team exposed normal mice and mice engineered to lack CPG15 to light and dark periods. In normal mice, there was much more PSD95 recruitment during the light phase than during the dark, but in the mice without CPG15, the experience of seeing in the light never made a difference in PSD95 recruitment. It was as if CPG15-less mice in the light were like normal mice in the dark.

Exogenous expression of CPG15 in the dark even recruited PSD95, as if the animals were exposed to visual experience. This showed that CPG15 not only carries the message of experience in the light, it can actually substitute for it in the dark.

■ In **Cell Reports,** CPG15/Neuritin Mimics Experience in Selecting Excitatory Synapses for Stabilization by Facilitating PSD95 Recruitment. Aug. 6, 2019. http://bit.ly/MIT-CPG15

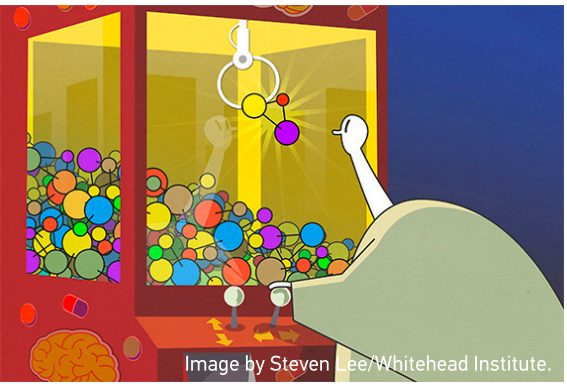


New research has led to a proposed model for how synapses become permanent: Fledgling synapses that respond to experience-driven neural activity gain CPG15, which recruits PSD95.

ABOUT THE COVER: The installation "Thought Assemblies" (1979-82, 2014) by artist and MIT alumnus Todd Siler guides visitors through representations of brain-related concepts via a structure shaped to mimic the limbic system. "Thought Assemblies" is part of MIT's and The Picower Institute for Learning and Memory's Art Collections. The colorful painting, titled "Prescience, Foresight" (1986-88), mounted in the hippocampus and amygdala area of this sculptural sketch is part of the permanent collection of The Metropolitan Museum of Art Twentieth Century Collection in New York.

Speeding up Drug Discovery for Brain Diseases

A research team of scientists at the Whitehead Institute and several members of the lab of Picower Institute faculty member Mriganka Sur has identified 30 distinct chemical compounds — 20 of which are drugs undergoing clinical trial or have already been approved by the FDA — that boost the protein production activity of a critical gene in the brain and improve symptoms of Rett syndrome, a rare neurodevelopmental condition that often involves autism-like behaviors in patients.



The new study, conducted in human cells and mice, helps illuminate the biology of an important gene, called *KCC2*, which is implicated in a variety of brain diseases, including autism, epilepsy, schizophrenia, and depression. The researchers' findings, published in the July 31st online issue of *Science Translational Medicine*, could help spur the development of new treatments for a host of devastating brain disorders.

KCC2 works exclusively in the brain and spinal cord, carrying ions in and out of neurons. This shuttling of electrically charged molecules helps maintain the cells' electrochemical makeup, enabling neurons to fire when they need to and to remain idle when they don't. If this delicate balance is upset, brain function and development go awry.

Lead author Xin Tang, a postdoc in the lab of Whitehead faculty member Rudolf Janiesch, and co-authors developed a technique to screen more than 900 chemical compounds, focusing on those that have been FDA-approved for use in other conditions, such as cancer, or have undergone at least some level of clinical testing.

Postdoc Keji Li of the Sur lab led behavioral experiments in mouse models of Rett Syndrome that were essential for revealing the potency of drugs identified and tested in the study.

"This work pushes the envelope for understanding and treating neurodevelopmental disorders in three ways," Sur said. "First, it uses human stem cell derived lines combined with genetic engineering to discover new therapeutic molecules for brain disorders such as Rett Syndrome. Second, it does so for a novel target of broad significance, namely a transporter which affects inhibition. Third, it uses cutting edge measurements to validate the newly discovered therapeutic molecules."

■ In **Science Translational Medicine**, Pharmacological enhancement of KCC2 gene expression exerts therapeutic effects on human Rett syndrome neurons and Mecp2 mutant mice. July 31, 2019, http://bit.ly/MIT-KCC2

New Algorithm Finds Neural Spikes in Flashing Lights

Neurons "speak" in patterns of electrical spikes that neuroscientists can tap to literally read animal and even human minds. But their methods for such eavesdropping are imperfect.

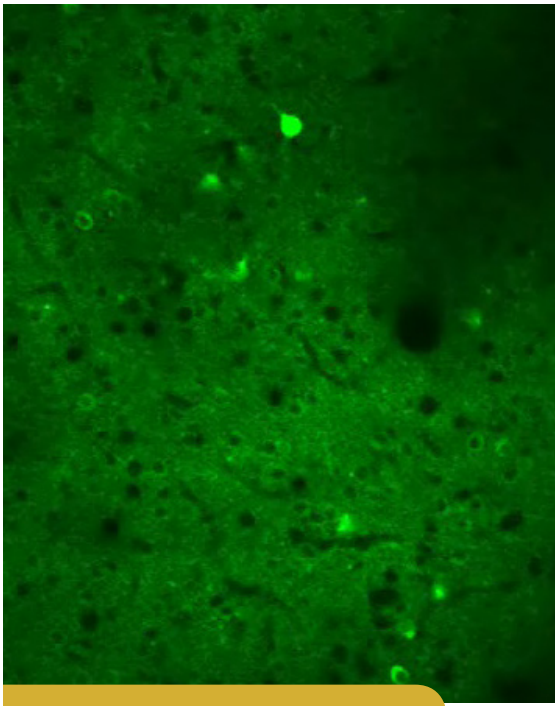
Poking electrodes into tissue is direct but it's invasive and doesn't reveal which cell has been sensed. Engineering neurons to flash with light when calcium levels peak is less invasive and shows the exact cell that's spiking, but it's an indirect indicator of electrical activity and quickly becomes muddled when flashes overlap. To improve how well the timing of spikes can be estimated from flashes, researchers at IIT Madras and MIT have developed a powerful algorithm with computational inspiration from the analysis of speech and music.

As reported recently in a paper in *IEEE Transactions on Signal Processing*, the team shows that the algorithm, called GDspike, often performs better than some other popular methods. Its greatest power, however, appears to be that when used in combination with a particularly successful model-based method called MLspike, it can improve analysis even more.

"GDspike performs reasonably well," said co-senior author Mriganka Sur, Newton Professor of Neuroscience in MIT's Picower Institute. "But in particular when you use modeling and then apply this on top of it, it performs really well. That is one of best ways to deconvolve signals to date."

Sur's lab constantly uses calcium fluorescence to track neural activity, for instance to study how neurons in different brain regions communicate to guide behavior. That's put him on the front lines of the problem of estimating spike patterns. Since working with the team of co-senior author Hema Murthy, Professor of Computer Science at IIT Madras, to develop GDspike, he said, he has begun combining it with MLspike to improve his lab's analysis of experimental data.

■ In **IEEE Trans. on Signal Processing,** Spike Estimation From Fluorescence Signals Using High-Resolution Property of Group Delay. June 1, 2019, http://bit.ly/GDspike



Neurons in the visual cortex of a mouse light up with calcium activity. Image by Ming Hu.

Analysis Bridges External, Direct Brain Recordings

With so many questions about how the brain works, scientists have developed multiple ways to measure neural activity. A psychiatrist might study patients using encephalography technologies like EEG or MEG that use external sensors. A neuroscientist might probe circuits more deeply and finely with electrodes implanted directly in the brain of an animal subject. But can what's learned in one kind of study help inform the other? In *eLife*, a team of scientists including Picower Professor Earl Miller establishes a bridge to help close the gap.

"A main benefit of this work is that by better mapping human EEG data to the insights we gain from direct circuit recordings in animals, we'll be able to help clinicians more finely interpret non-invasive recordings they make with patients," Miller said. "The missing link, so to speak, between them was what we learned from EEG data in animals."

Miller collaborated with a team at Tübingen University led by former postdoc Markus Siegel, who is now a professor at the German institution. They had non-human primates and human volunteers perform the same simple perception task. In humans they recorded neural activity with MEG; in the animals they recorded with EEG very similarly to how they would in humans and also used microelectrodes in six regions of the brain to directly record the activity of thousands of individual neurons.

Then they analyzed the recordings to determine where they shared similar information. All three recordings contained information about neural representations of movement and color. The animal EEG bridged the gap between direct and human MEG recordings because the analysis revealed signals in the animal EEG that corresponded to the direct electrode recordings, and it also identified signals in the human MEG that matched the animal EEG. The analysis also helped to clarify where measurements among the three techniques did not map well to each other.

■ In **eLife**, Monkey EEG links neuronal color and motion information across species and scales. July 9, 2019, http://bit.ly/EEG-link.

Team Distinguishes 4 Neuron Types in Spike Data

For decades, neuroscientists have relied on a technique for reading out electrical "spikes" of brain activity in live, behaving subjects that tells them very little about the types of cells they are monitoring. In a new study, researchers at the University of Tübingen and MIT's Picower Institute demonstrate a way to increase their insight by distinguishing four distinct classes of cells from that spiking information.

The advance offers brain researchers the chance to better understand how different kinds of neurons are contributing to behavior, perception and memory, and how they are malfunctioning in cases of psychiatric or neurological diseases. Much like mechanics can better understand and troubleshoot a machine by watching how each part works as it runs, neuroscientists, too, are better able to understand the brain when they can tease apart the roles different cells play while it thinks.

"We know from anatomical studies that there are multiple types of cells in the brain and if they are there, they must be there for a reason," said Earl Miller, Picower Professor of Neuroscience in the Department of Brain and Cognitive Sciences at MIT, and co-senior author of the paper in *Current Biology*. "We can't truly understand the functional circuitry of the brain until we fully understand what different roles these different cell types might play."

Miller collaborated with the Tübingen-based team of lead author Caterina Trainito, Constantin von Nicolai and Professor Markus Siegel, co-senior author and a former postdoc in Miller's lab, to develop the new way to wring more neuron type information from electrophysiology measurements. Those measures track the rapid voltage changes, or spikes, that neurons exhibit as they communicate in circuits, a phenomenon essential for brain function.

"Identifying different cell types will be key to understand both local and large-scale information processing in the brain," Siegel said.

■ In **Current Biology**, Extracellular Spike Waveform Dissociates Four Functionally Distinct Cell Classes in Primate Cortex. Aug. 22, 2019, http://bit.ly/four-cells.

Chung Earns Top U.S. Government Honor for Young Scientists

Kwanghun Chung, associate professor in The Picower Institute for Learning and Memory, the Department of Chemical Engineering and the Institute for Medical Engineering and Science, received a Presidential Early Career Award for Scientists and Engineers July 25 at the White House.

A PECASE is the nation's highest honor for young scientists and engineers.

"Established in 1996, the PECASE acknowledges the contributions scientists and engineers have made to the advancement of science, technology, engineering, and mathematics education and to community service as demonstrated by scientific leadership, public education, and community outreach," the Trump Administration said in a statement announcing the award July 2. "The White House Office of Science and Technology Policy coordinates the PECASE with participating departments and agencies."

Chung's nomination, recognizing a series of innovations in tissue processing that has allowed for revolutionary new views of the brain at multiple scales, came from the U.S. Department of Health and Human Services.

Chung, who is also appointed in the Department of Brain and Cognitive Sciences, said he credits his whole team for the award.

"I am extremely honored and grateful for this recognition," he said. "This award was only possible thanks to my team's exceptional work and dedication. I'm infinitely grateful to be a part of such an amazing team and we hope our research can contribute to expediting discoveries and ultimately, improving human health."

Chung received his B.S. in Chemical Engineering from Seoul National University in 2005, and then moved to Georgia Institute of Technology for his Ph.D. training, where he developed automated and integrated microsystems for high-throughput imaging, molecular/behavioral phenotyping, and cell microsurgery of a broad range of living systems.

After Georgia Tech, Chung joined the Karl Deisseroth Lab at Stanford University for post-doctoral training, where he invented a novel technology termed CLARITY, which enables system-wide structural and molecular analysis of large-scale intact biological samples. In 2013, Chung joined the MIT and Picower Institute faculty to lead an interdisciplinary team in developing and applying novel technologies for holistic understanding of large-scale complex biological systems such as the brain.

He has continued to invent a series of innovative tissue engineering technologies including MAP, SWITCH, Stochastic Electrotransport and most recently SHIELD.

These tools enable neuroscientists to clear brain tissue, enlarge it, label and preserve it so that it can be imaged to reveal not only physical structure, but also protein expression. Last year he and collaborators earned a major NIH grant to make the most comprehensive map ever of the entire human brain. That work is now underway.

> We hope our research can contribute to expediting discoveries and ultimately, improving human health.
>
> *Kwanghun Chung*

Morgan Sheng Returns to MIT; Joins Broad Institute

Morgan Sheng, who served as a faculty member in the Picower Institute between 2001 and 2008 before building the neuroscience department of the pharmaceutical company Genenetech, has returned to Cambridge.

In May he began his new role of co-director of the Stanley Center for Psychiatric Research at the Broad Institute. Sheng will help to shape the center's scientific vision and direction, and oversee the center's efforts to develop therapeutics for schizophrenia and other serious mental illnesses.

He is an author of more than 200 peer-reviewed publications focused on the molecular mechanisms underlying the structure and plasticity of synapses and the molecular-cell biology of neurodegeneration.

Now with his return to MIT, Sheng has also reunited with the Picower Institute as an affiliate member. He also has a new appointment as a professor in the department of Brain and Cognitive Sciences.

JPB Foundation Gift Extends Fellowship Programs

Postdoctoral scholars are not only crucial contributors to neuroscience research at The Picower Institute for Learning and Memory right now, but also they are the future of the field. A new gift from The JPB Foundation will ensure a bright future for two fellowship programs that advance the career growth of postdocs.

The gift renews support for the Picower Fellows program, which fully supports a highly promising postdoc in each Institute lab and provides each of those fellows with career development and networking opportunities. It also extends the Picower Clinical Fellowships, in which Boston-area physicians are funded to dedicate 80 percent of their time to research in The Picower Institute for Learning and Memory. They thereby gain extraordinary fundamental insight into neurological and psychiatric conditions and also strengthen connections between neuroscience research and clinical care. The gift will increase the number of clinical fellows from one to three.

"As young professional researchers, postdocs represent the next generation of professors, physician-scientists, industry research leaders and mentors for the field," said Institute Director and Picower Professor Li-Huei Tsai. "It is therefore a huge contribution to the global scientific enterprise to identify the most promising postdocs and to provide them with the support that will ensure they thrive both today and tomorrow. By generously supporting The Picower Fellows program and the Picower Clinical Fellowships, The JPB Foundation is making a substantial impact on neuroscience that will last for generations."

IMPORTANT IMPACT

For example, the Tsai Lab's Picower Fellow, Chinnakkaruppan Adaikkan was the lead author of a paper in *Neuron* in May demonstrating key advances for a non-invasive method for stimulating the senses to potentially combat Alzheimer's disease, called GENUS. The research showed that in multiple mouse models of the disease, exposing mice to light flickering at the 40Hz frequency of gamma rhythms in the brain significantly stemmed the advance of disease pathology, prevented neurons from dying and preserved learning and memory. In late 2018, meanwhile, Picower Fellow Hyeseung Lee in the lab of Associate Professor Myriam Heiman co-led a paper in *Cell Reports* showing that amid oxidative stress some aging neurons became plagued with a potentially harmful buildup of RNA fragments. And, Mikael Lundqvist, a former Picower fellow in the lab of Picower Professor Earl Miller, recently co-authored a paper proposing a new model of how working memory functions (see cover story) with Miller, published in the 30th Anniversary issue of *Neuron*.

While the fellowship funding allows the postdocs to focus on research, special programs provide knowledge and experience that can help them become successful independent researchers. This includes not only mentoring in their labs, but also talks and advice on seeking jobs in academia and managing the finances of an independent lab. They also practice presenting their work at symposia and other events.

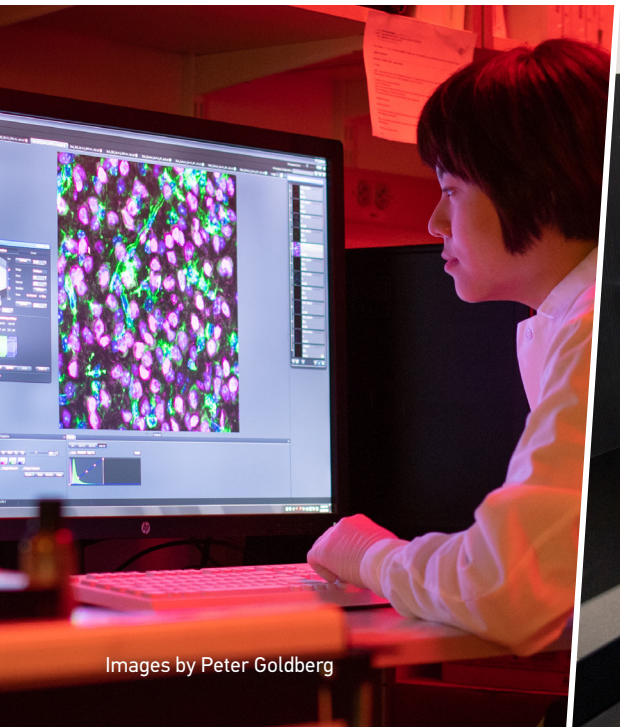
In all, nearly 40 postdocs have participated in the program since it began five years ago.

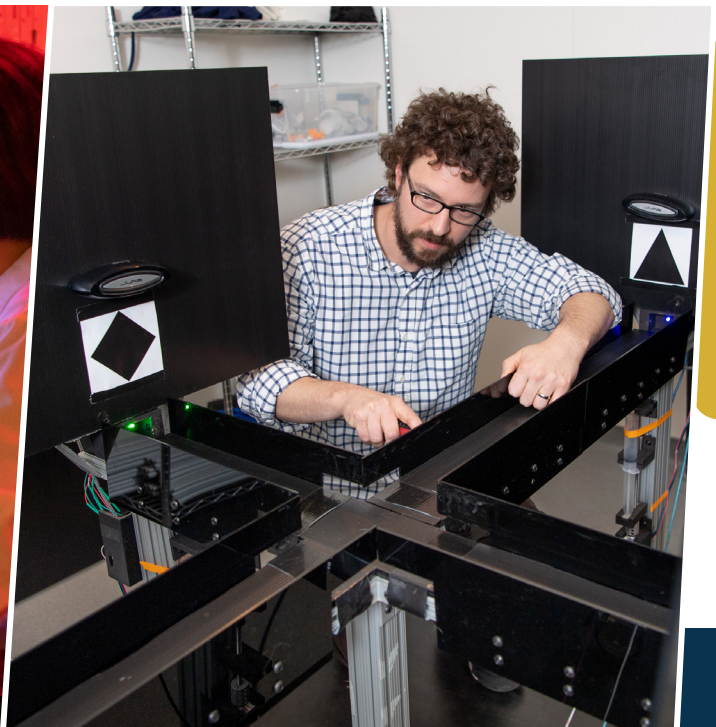
CLINICAL CONNECTIONS

The Picower Clinical Fellows program recently welcomed its fifth participant, but it has already demonstrated a variety of valuable outcomes. As the inaugural Picower Clinical Fellow, psychiatrist Michael Halassa worked in the lab of Professor Matthew Wilson, Sherman Fairchild Professor of Neurobiology, to probe the crucial connections between the cortex and the thalamus. Last year he returned to MIT as a faculty member where he now leads a lab that has published several notable new studies. Miller, meanwhile, has published two papers in the last six months with his former clinical fellow Alik Widge, now an assistant professor at the University of Minnesota. Most recently, pediatrician Ravi Raju's work in the Tsai lab has helped to nucleate new research in the Institute focused on the neurobiology of early life stress.

PILM's newest fellow, Diane Chan, is a neurologist at Brigham and Women's Hospital in Boston. She is leading the team in Tsai's lab that is testing the crucial question of whether GENUS can help humans with Alzheimer's Disease.

"Advances against disease come from research," Chan said. "Using GENUS to combat disease is a truly innovative concept that has led to a translational project that will let us see if this will help patients with dementia. Coming to MIT to work on this project is an incredibly exciting opportunity. I'm grateful that the support of the Picower Clinical Fellowship will be a huge help in sustaining our ongoing work."





Images by Peter Goldberg

LEFT: Picower Fellow Hyeseung Lee examines an image from the confocal microscope in the lab of Associate Professor Myriam Heiman.

RIGHT: Picower Fellow Tim Brawn sets up a maze for rats in the lab of Sherman Fairchild Professor Matthew Wilson.

Memory and its Meaning

Over 25 years, Picower Institute researchers have made major advances in what we know about memory

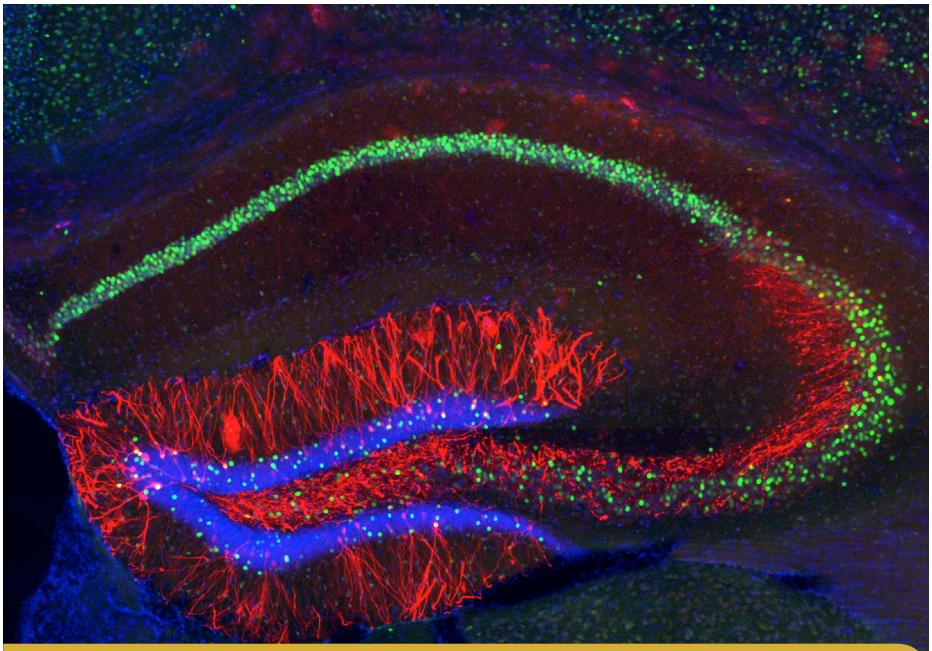
Lest anyone forget, in 1994 when MIT launched a Center for Learning and Memory that would later become The Picower Institute for Learning and Memory, the then Provost Mark S. Wrighton promised: "MIT has given high priority to the neurosciences because we believe that an effort in basic science now will yield major progress in understanding the biological origins of complex brain functions. ...Such understanding would provide unparalleled insights into the nature of the human mind."

Since then, a quarter century of rigorous, innovative MIT research on the nature of memory has substantiated that pledge. While huge and tantalizing questions remain, Picower Institute researchers have made major contributions to the field's understanding of how memory works and how the brain uses memory to survive and thrive. They have mastered the molecular, cellular and circuit mechanisms of memory systems enough to demonstrate groundbreaking feats of mind reading, memory restoration and even memory manipulation in animals. They have revealed profound intersections of memory and behavior, and explained how we consciously use memory.

Once investigated only as a psychological phenomenon of mind, memory is now also studied biologically and physically, said Picower Professor Susumu Tonegawa, who founded the center (CLM) in 1994 and became the Picower Institute's inaugural director. That level of inquiry provides a mechanistic foundation for better understanding psychiatric and neurological disorders.

"By identifying at the cellular level where information is stored, the next stage is that we can use the function of these cells to overcome deficiencies," Tonegawa said.

The new depth of insight has also allowed neuroscientists to study how the brain employs memory in intelligent behavior, said Matt Wilson, associate director of the Picower Institute.



In this image produced by Xu Liu and Steve Ramirez in the lab of Picower Professor Susumu Tonegawa, red labeled cells compose the physical traces of memory, or engrams. The image appeared on the cover of Science in July 2013.

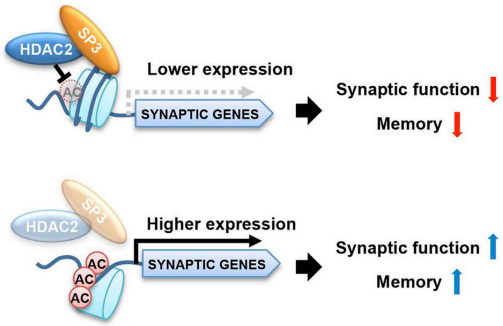
"The primary function of memory in biological systems is to understand the meaning of information, not just to store its content," said Wilson, the Sherman Fairchild Professor of Neurobiology.

Memory Machinery

Tonegawa helped to usher in the physiological science of memory in 1992 when he and colleagues became the first to employ a genetic manipulation to demonstrate the pivotal role of a gene in memory formation. In mice, the scientists "knocked out," or deleted, the gene alpha CaM kinase II, which enables neurons in the hippocampus to form and strengthen connections with other neurons. Mice missing the gene failed to learn key locations in a maze.

At the time, knocking out genes was cutting edge, but also relatively crude. The CaMkII deletion occurred all over the mouse body. Neuroscientists gained the ability to target specific regions or cell types. In 1996, for the first time, a knockout was targeted to a specific cell type in a specific brain region: the NMDA receptor gene in hippocampus area CA1 pyramidal cells. In this way, Tonegawa and Wilson demonstrated that the gene is crucial for spatial memory coding and acquisition. In 2002, Tonegawa and Wilson further showed that a gene for the NMDA receptor was necessary in hippocampus area CA3 for mice to be able to retrieve spatial memories efficiently.

Neuroscientists have also become deft at editing genes and inserting new ones. In



A diagram from research by Picower Professor Li-Huei Tsai explains that interfering with the activity of the proteins HDAC2 and SP3 can increase gene expression related to synaptic function and memory.

"optogenetics," for example, genetic insertions enable neurons to become active or inactive in response to different colors of light.

"As work went on, the questions you could ask became more and more precise and specific," Tonegawa said. "This opened up a new way to study memory in the brain."

In 2012, Tonegawa's lab was also the first to show that by labeling genes activated early in memory formation, they could pinpoint the ensemble of a hippocampal "engram," the neurons that encoded a specific fear memory. How did they know? Because when they optogenetically activated the ensemble, the mouse froze as if recalling that fearful episode.

In subsequent studies, Tonegawa's lab achieved other marvels of manipulation that demonstrate how memory is situated and structured in the brain. In one, the lab created a false memory by artificially reactivating the engram of a previously experienced place while giving the mouse a little shock. Mice then exhibited a fearful response in that place, even though they hadn't actually experienced the shock there.

In a paper relevant to PTSD and anxiety, Tonegawa's lab flipped the emotional association of memories. For instance, they gave a mouse a little shock in a context, initially conditioning fear. But then, when they reactivated the engram of that context while presenting a reward, the cells rewired their connection to the amygdala, a region that governs feelings, to produce a more positive association. The researchers also did the opposite, swapping an engram's positive association for a fearful one.

In 2015, the lab highlighted the distinction between memory storage and recall. They showed that if they weakened the protein synthesis that enable engram cells to strengthen connections, or synapses, they could block a mouse's ability to recall a memory. But if they artificially activated the engram they could still produce recall. The study demonstrated that synaptic strength may determine whether a memory is accessible, but the mere pattern of connections among the cells was enough to store it. In 2017, they reported that memory engram cell ensembles are simultaneously formed in the hippocampus and in the cortex immediately after an experience, challenging the widespread assumption that the episodic memory is first stored in the hippocampus and related brain regions, but the storage site shifts to the cortex only subsequently. This finding generated a new concept of "silent memory," a memory state that cannot be retrieved efficiently by natural recall cues.

A simultaneous area of advancement has been observing and controlling "epigenetics," the set of molecular factors that modify how genetic information is "expressed," or implemented by cells. The lab of Picower Professor and Institute Director Li-Huei Tsai has used these advances to understand and improve memory storage and recall. Tsai, who studies neurodegenerative memory disorders such as Alzheimer's disease (AD), has since helped to translate her insights into strategies to develop potential therapies.

> You can define memory based upon what's left in the brain after you take away the world.
>
> *Matthew Wilson*

In 2006, just as she was joining the Picower Institute, Tsai's lab showed that placing AD model mice in a more mentally stimulating environment improved their flagging memory recall. The team sought the molecular mechanism. In mice that experienced enrichment, they observed, genes associated with synaptic function in learning and memory were in a more physically accessible state for expression, compared to the same DNA in unenriched animals. They then showed that by chemically inhibiting proteins responsible for locking down DNA, called HDACs, they could mimic enrichment's benefits and improve memory recall.

"That was pretty neat because seemingly lost memories were not really lost," Tsai said. "You could do something to get it back."

In subsequent papers, the researchers advanced their understanding. In 2009, they determined that HDAC2 was the specific HDAC responsible and in 2012 they showed that Alzheimer's pathology misregulates HDAC2, indicating one way the disease disrupts memory. In 2017 they found that they could inhibit HDAC2 specifically by inhibiting a co-factor called sp3. That finding pinpoints the specific nuclear complex that targets memory gene expression and helps to guide the pursuit of potential drugs to enhance memory while minimizing unintended effects on other HDACs.

Tsai's investigation of gene expression in AD generated a surprising finding about the speed of memory formation. Her lab had observed that in many AD models, neural DNA showed the severe damage of double-strand breaks (DSBs) so the lab set out to induce DSBs in neurons to see how they affected gene expression. In 2015 Tsai and colleagues discovered that DSBs are necessary for the expression of genes that are expressed at the very beginning of memory formation. They essentially snap open DNA for rapid expression when activated by a memorable stimulus. In healthy mice, the breaks are repaired within hours. In AD, Tsai hypothesizes, the breaks are not repaired well, potentially leading to neural damage and death.

Memory Meaning

Like Tonegawa, Wilson has long been interested in pinpointing and studying specific memories in the hippocampus but does it differently. Beginning as a postdoc in Arizona in the early 1990s and continuing to this day, Wilson has pioneered methods of eavesdropping on and interpreting the electrical activity, or "firing," of neurons to discern what that chatter of rising and dropping voltages encodes. Via these methods, Wilson's lab can read out the location in a maze that a rat is remembering within mere millimeters. Last year, in fact, he and former postdocs showed they could read such thoughts almost in real-time.

Wilson's goal has been to understand how memories become meaningful in intelligent behaviors such as pursuing reward.

He arrived at MIT and the CLM in 1994 just as he led a seminal paper showing that the same ensembles of hippocampal neurons in rats that would fire as the rat ran a maze, would also fire in the same patterns while the rat was asleep. Capturing this memory "replay" in action was a powerful demonstration that substantiated the hypothesis that memory is consolidated during sleep.

Sleep is an ideal condition for memory research, Wilson notes, not only because of its consolidation role but also because in the absence of stimulation or experience, whatever information the brain is processing can easily be recognized as memory.

"You can define memory based upon what's left in the brain after you take away the world," Wilson said.

Over time, Wilson's work on memory replay has shown a great deal about what "processing" means. In a pair of papers in 2001 and 2002, for example, he showed that while memory replay in sleep's REM phase occurs in long stretches almost like the timescale of real experience, replay in slow-wave sleep occurs at about 20 times speed and is broken up into short snippets.

In 2009 Wilson's lab showed that rats replay memories of their journeys even while awake, during resting moments along the way. Given a moment to think, rats consider their environs, including remote parts of the maze. Notably, they even replay the maze in reverse, as if retracing their steps.

Like in slow-wave sleep, the team found, memories were replayed rapidly and in small snippets, even as their order in time was preserved. Wilson hypothesizes that in these reflective moments the brain may be considering how fundamental units of experience can be regarded, understood and recombined for other uses.

"The idea that sleep carries some function is a mystery of memory," Wilson said. "What goes on in these offline periods of introspective evaluation that contribute to higher level functions like creativity, insight and wisdom? How might that be accomplished? Decomposing and recomposing experience is attractive, and finding explicit neural correlates of this is supportive of this idea."

Picower Professor Earl Miller joined the ranks of the CLM in 1995. He studies higher-level cognition where memory is put to use. Miller's lab, for instance, examines how the brain sorts objects into categories, a feat that requires combining new sensory information with prior experience (i.e. the meaning of memory). Miller also studies the special system of working memory. The "sketchpad of consciousness," working memory is how people intentionally select and manipulate information – both remembered and new – to accomplish tasks. It's how, for instance, one formulates a plan for the day.

"When I first started the lab 25 years ago, the working memory task of holding something in mind for a while was the highest level cognitive phenomenon people were studying, but that's all they were studying," he said. "To me, the main story is how the animal knows to do what you told it to do. Nobody was studying that."

Miller lab's blends precise measurements of neural activity with measurements of broad scale brain oscillations, which are the rhythms that synchronize neurons to work together. The team focuses on areas of the cortex that process new sensory information as well as areas, like the prefrontal cortex, that engage in cognitive information processing.

Miller's lab observed that sensory information is encoded among cortical neurons by high-frequency "gamma" rhythms, while the learned understanding of patterns that allow for categorizing a new object are encoded by lower-frequency "beta" rhythms. Meanwhile in 2014, a young Swedish neuroscientist named Mikael Lundqvist developed a computational model to hypothesize a way that working memory could hold multiple bits of information simultaneously in mind. He posited that oscillations occur in brief bursts, rather than persistently, with beta rhythms controlling gamma ones.

Walking to work one day, Miller realized that Lundqvist's model squared well with his observations and predicted several working memory phenomena. Lundqvist joined the lab in 2015 and in a flurry of recent papers, Miller's team has since experimentally confirmed many aspects of the model.

A grand culmination came in 2018 in the form of a new model of working memory. Governed by the memories and goals encoded in bursts of beta rhythms from neurons in deeper layers of the cortex, gamma waves encode new sensory information for consideration and juggle multiple (but limited) items of information in mind for processing. This hierarchical blending of bursts explains several phenomena that the orthodoxy of persistent activity does not, Miller said.

The model, dubbed "Working Memory 2.0," could aid research on schizophrenia, where working memory is known to founder.

In the visual cortex (V1), Picower Professor Mark Bear's lab has found the site of a fundamentally important type of memory that impacts behavior. "Visual recognition memory" helps us account for what we've already seen so that we are better able to focus on what's new.

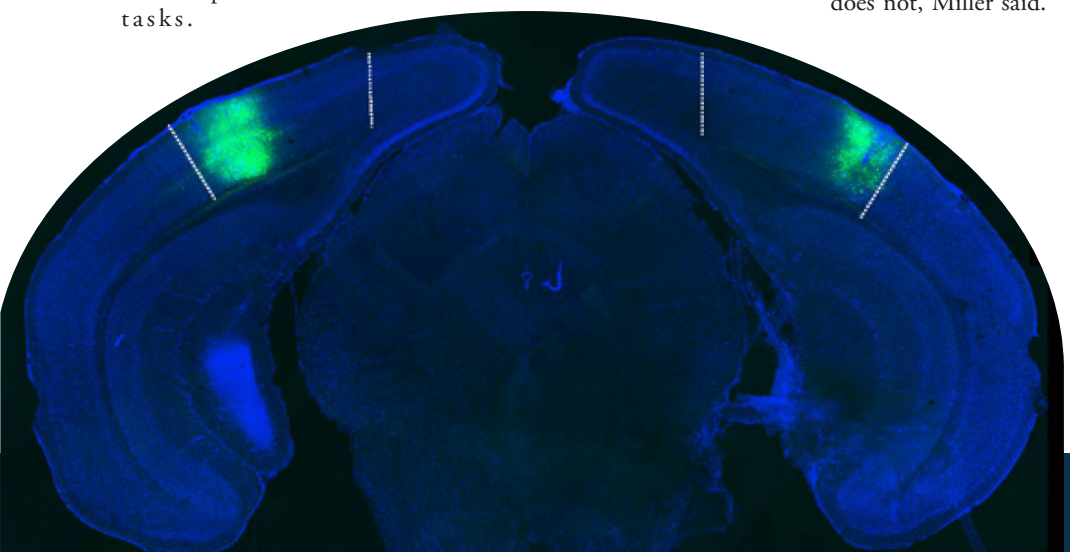
"We rely very much on our ability to detect novelty in a sea of familiarity," he said. "To pick out the novel stimulus you have to have already formed a memory of what's familiar."

Notably, Bear said, this kind of memory appears to be disrupted in conditions like autism and schizophrenia.

Bear confesses that the discovery was somewhat of an accident. His then graduate student Nate Sawtell was trying to assay visual responses in V1 of awake mice when he encountered something confusing. Mice shown the same visual pattern every day produced a steadily increasing electrophysiological response in layer 4 of V1. When he tried a novel pattern, the response was back at the initial baseline level. Bear ultimately called this phenomenon "stimulus-selective response potentiation" or SRP.

In a paper in 2015, the lab showed what SRP meant. Mice are so excited by new visual patterns they will try to explore them. This behavioral response diminishes, or habituates, over days as the once novel pattern becomes familiar and SRP emerges in V1. The team went on to show that by blocking in V1 various synaptic processes and receptors – the same protocols that can be used to disrupt SRP – they could prevent habituation. In other words, the ability the mice developed to recognize and ignore familiar stimuli was based the ability of the visual cortex to form a visual recognition memory.

Whether it serves to help us recognize what's new or as the basis of all that we know, memory's importance as a subject of neuroscience research remains undeniable. The progress evident in 25 years of Picower Institute research has helped to ensure that even more progress will follow in the years ahead.



A cross-section of a mouse's brain reveals areas of the visual cortex where Picower Professor Mark Bear's lab manipulated receptors to study Visual Recognition Memory.

Memory Futures

How do Picower Institute labs plan to continue their progress studying memory systems? What new questions motivate them the most? We put these questions to four professors in the institute. They laid out a fascinating forecast.

Mark Bear

"On visual recognition memory we are now collaborating with Chuck Nelson at Boston Children's Hospital because he is a pioneer in looking at evoked potentials (neural signals) in infants that are at risk for autism… So we did a pilot study in human young adults measuring visual evoked potentials and eye movements as they look at the same patterns as the mice. The VEP does change and eye movements also reveal a habituation – just like we observe in mice. Now we are repeating the studies in human infants. Ultimately our objective is to see if this process is disrupted in infants at risk for autism. And in our lab we are looking at genetically defined causes of autism to see how the process might be disrupted – and if we can fix it."

Earl Miller

"In terms of 'Working Memory 2.0' we want to do things like manipulate cortical rhythms so we can a) test our hypotheses in a stronger way but b) we want to see if we can actually improve cognition… Think of the interplay of beta rhythms (representing goals) and gamma (representing sensory inputs) as a continuum. Sometimes you are very task oriented and focused to ignore distractions – that's a beta mode. Other times you are more open and receptive – that's more of a gamma mode. Now imagine we can manipulate these rhythms – you can dial in whichever mode is optimal for whatever you are doing. Anyone can screw up the brain. Improving the brain is more of a challenge."

Matt Wilson

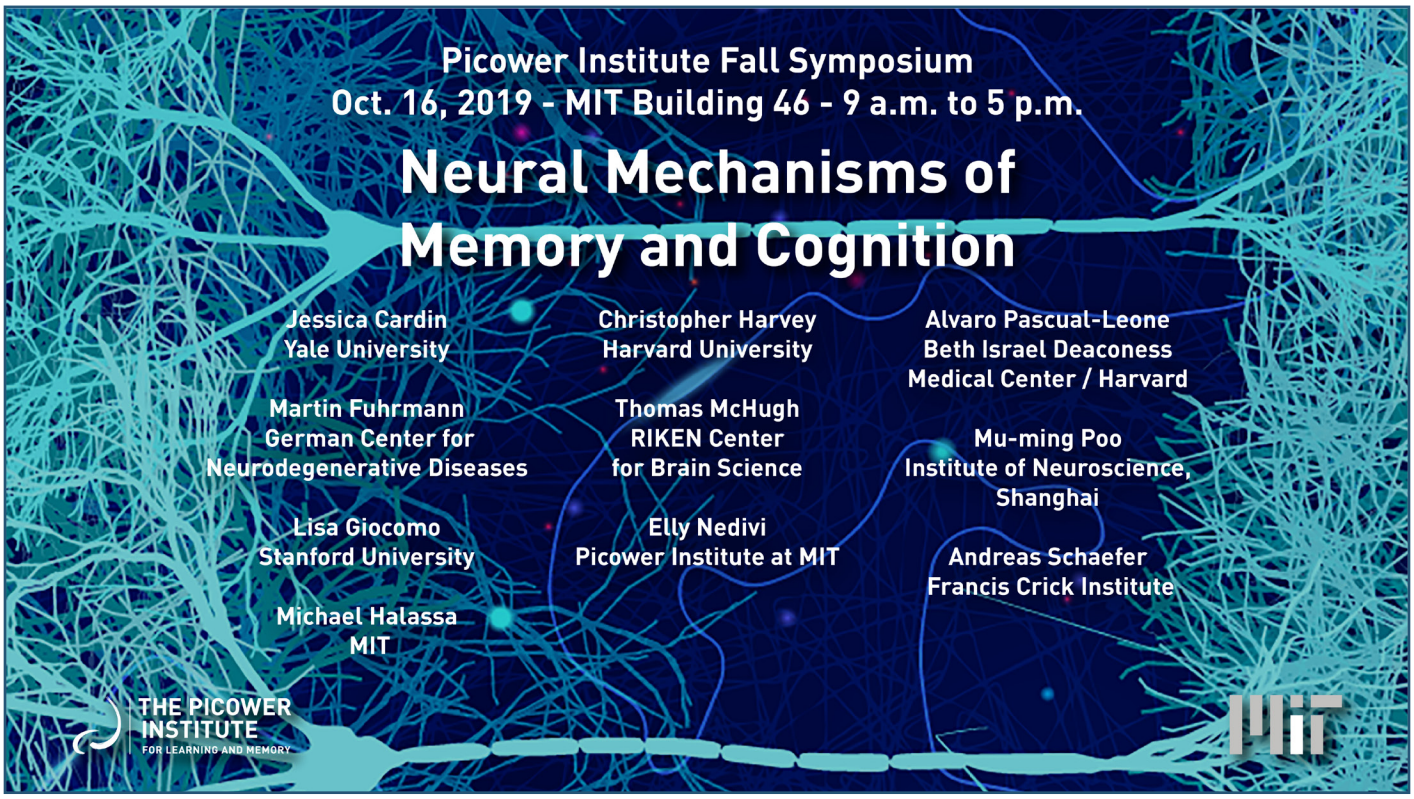
"It really is the connection between memory, learning and intelligence. How are we able to learn about the world through simple experience in ways that allow us to solve problems in what would appear to be near optimal fashion. That's what intelligence is… We experience the world and somehow we are able to survive, thrive, adapt and create and not just do the things we've already done, but to also do things we've never done… Memory is tied to that. Memory both exists to drive retrospective evaluation about what we've done in the past but also to drive prospective thinking of what we might do in the future. The interest is in how the brain creates and drives models of the future."

Susumu Tonegawa

"In order to apply the currently available technology to study memory, much of the advances are being made in animal models. We have a strong belief that the fundamental principles operating in the brain including for memory applies between animals and humans. On the other hand, obviously humans are higher mammals in whom cognitive functions are more sophisticated. There are some cognitive functions that are very difficult to study in animals… Future studies of brain research and memory research will certainly require the development of much more sophisticated technology. After all, we want to understand how the human brain works."

Upcoming **EVENTS**

For the *latest* information on all our lectures, symposia and other events, please visit: **picower.mit.edu/events**



Save the date - Nov. 6, 2019, 1p.m. - 6 p.m.

Inaugural Alana Down Syndrome Center Symposium

Translational Research in Down Syndrome

alana Down syndrome center

Keynote speakers

- **Roger Reeves,** McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University
- **Joaquin Espinosa**, Linda Crnic Institute for Down Syndrome, University of Colorado

Picower Institute - MIT Building 46

Upcoming Seminars and Colloquia

All talks take place at 4 p.m. in Singleton Auditorium, MIT Building 46 unless otherwise noted

10.07.19
Aging Brain Seminar with Bing Ren
LUDWIG INSTITUTE

10.10.19
Colloquium with Vanessa Ruta,
THE ROCKEFELLER UNIVERSITY

11.05.19 (at 10 a.m.)
Aging Brain Seminar with Jerold Chun
SANFORD BURNHAM PREBYS MEDICAL DISCOVERY INSTITUTE

11.14.19
Colloquium with Thomas Clandinin
STANFORD UNIVERSITY

11.21.19
Colloquium with Matthew Diamond
INTERNATIONAL SCHOOL FOR ADVANCED STUDIES, SISSA

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Massachusetts Institute of Technology
77 Massachusetts Avenue Building 46 Room 1303
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The Picower Institute is a community of scientists dedicated to understanding the mechanisms that drive learning and memory and related functions such as cognition, emotion, perception, and consciousness. Institute researchers explore the brain at multiple scales, from genes and molecules, to cells and synapses, to circuits and systems, producing novel insights into how disruptions in these mechanisms can lead to developmental, psychiatric, or neurodegenerative disease.

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EDITORIAL CONTRIBUTORS

David Orenstein and Nicole Davis.

CONTACT THE PICOWER INSTITUTE

The Picower Institute for Learning and Memory
Massachusetts Institute of Technology,
77 Massachusetts Avenue, Building 46, Room 1303,
Cambridge, MA 02139-4307, Tel: 617-324-0305 picower.mit.edu

TOP ROW: **Mark F. Bear**, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Investigator, Howard Hughes Medical Institute (HHMI); **Emery Brown**, Edward Hood Taplin Professor of Computational Neuroscience and Health Sciences & Technology, The Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology; **Gloria Choi**, Samuel A. Goldblith Career Development Assistant Professor of Applied Biology, Department of Brain and Cognitive Sciences; **Kwanghun Chung**, Assistant Professor, Departments of Chemical Engineering and Brain and Cognitive Sciences, Institute of Medical Engineering and Science core faculty; **Steven Flavell**, Lister Brothers Career Development Assistant Professor of Neuroscience, The Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology; **Myriam Heiman**, Associate Professor of Neuroscience, Department of Brain and Cognitive Sciences, Broad Institute core member; **Troy Littleton**, Menicon Professor of Biology and Neuroscience, Departments of Biology and Brain and Cognitive Sciences.

BOTTOM ROW: **Earl Miller**, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences; **Elly Nedivi**, William R. (1964) & Linda R. Young Professor of Neuroscience, The Picower Institute for Learning and Memory, Departments of Brain and Cognitive Sciences and Biology; **Mriganka Sur**, Paul E. Newton Professor of Neuroscience, Director of The Simons Center for the Social Brain; **Susumu Tonegawa**, Picower Professor of Biology and Neuroscience, Departments of Brain and Cognitive Sciences and Biology, Investigator, Howard Hughes Medical Institute, Investigator and Director of the RIKEN-MIT Center for Neural Circuit Genetics; **Li-Huei Tsai**, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Director, The Picower Institute for Learning and Memory; **Matthew Wilson**, Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology, Associate Director, The Picower Institute for Learning and Memory.

Choi photo by Justin Knight