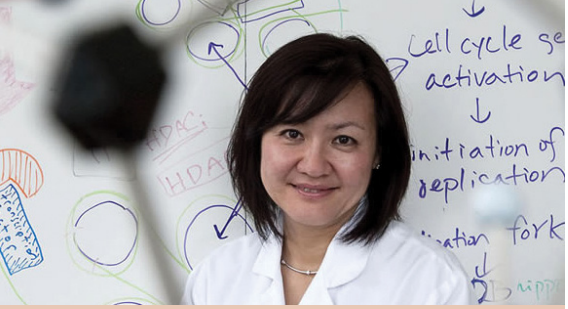
# Many Mechanisms of MOOD

**Picower Institute studies reveal a number of ways moods emerge in the brain and therefore many potential paths to address mood disorders. Pg. 8**

# Neuroscience News

FALL 2025

THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY




## DIRECTOR'S **MESSAGE**

Dear Friends,

Disorders of mood—depression, anxiety, bipolar disorder—are shockingly common. Most of us probably know a friend or family member who is one of the nearly 10 percent of U.S. adults who statistics suggest will experience a mood disorder in a given year.

A striking aspect of our cover story (page 8) is the variety of research roads that have led four labs to studies of mood. Susumu Tonegawa investigated how memories become associated with emotion, but Gloria Choi arrived at the exact same population of neurons by studying how the brain and immune system communicate. And while Emery N. Brown is looking at how anesthesia might encourage vast brain networks to reconfigure, Elly Nedivi's studies led to bipolar disorder because of small mutations in a specific gene.

The good news about the incredible complexity of how moods arise in the brain is that we can indeed find many avenues to exploit to try to affect them. Though mood disorders sometimes have proven difficult to diagnose and treat, we're still finding new leads.

We can't let the brain's complexity prevent us from helping people who are battling disease. On this page you'll see news of a new round of grants from our Aging Brain Initiative to stimulate Alzheimer's disease research across MIT. From investigations of important molecules to a sweeping national survey, these projects reflect the multifaceted challenges of neurodegeneration and illustrate our commitment—and that of many generous donors—to tackle them head on.

Our news pages feature many other advances. Earl Miller led a discovery of how very different anesthetic drugs end up achieving the same effect (p. 3). Not only has Mriganka Sur's lab published two studies about how vision develops and is sustained in the brain (p.4), but also worked with engineering colleagues to develop a new microscope—enhancing the vision of fellow researchers (p.5).

Though the focus on mood disorders in our cover story might seem gloomy, the research advances we report are encouraging. So long as we can do research, progress is always possible. We'll keep working to find the insights to help people in need.

**LI-HUEI TSAI, DIRECTOR**

*The Picower Institute for Learning and Memory*

# Aging Brain Initiative funds new **neurodegeneration** research

To help meet a variety of the challenges posed by neurodegenerative diseases, MIT's Aging Brain Initiative (ABI) has awarded seed grants for five innovative research projects across campus.

"The Aging Brain Initiative is a collaborative effort at MIT to advance our understanding of the complexities of the aging brain and Alzheimer's disease (AD)," said Picower Professor Li-Huei Tsai, director of the ABI and The Picower Institute for Learning and Memory and a faculty member in the Department of Brain and Cognitive Sciences (BCS). "The ultimate mission is to deliver the foundational research that addresses the challenges of brain aging and creates a better future for millions."

Pattie Maes, Germeshausen Professor of Media Technology in the Media Lab, has developed a wearable, voice-powered AI assistant that seniors can use to provide personalized reminders and aid in information recall. Maes will use her ABI seed grant to further refine the technology and then test it in real-world use during a four-week study among residents at senior living facilities in the Boston area.

Chemistry Associate Professor Bin Zhang plans an integrated analysis of molecular biology data, including alterations in gene expression, the accessibility of DNA for transcription, and three-dimensional DNA structure. Zhang will use his grant to develop a new AI-powered multimodal model to establish causal links across these data sets and reveal how the disease affects the operations of genes.

Mechanical Engineering Associate Professor Giovanni Traverso, Karl Van Tassel (1925) Career Development Professor, and MIT-Novo Nordisk AI Fellow Adrian Noriega de la Colina will extract key lessons from a long-term study in Finland in which seniors have undergone a suite of lifestyle and health interventions in hopes of preventing cognitive decline. The pair will analyze proteins in blood samples taken from participants at various timepoints of the 11-year study to pinpoint predictive protein level changes.

Lifestyle factors such as education, diet, exercise and social connection can have protective effects against the onset of AD and other dementias. An open question, however, is how much the general public knows about these possibilities. With their ABI seed grant, a team led by Joe Coughlin, director of the MIT AgeLab, will conduct a major national survey of U.S. adults of all ages to assess awareness.

Some people who have remained healthy despite harboring genetic mutations that typically would predispose them to developing AD exhibit key differences in how certain sugars, called heparan sulfate proteoglycans, interact with proteins. To understand how these sugars affect and protect brain health, Novartis Professor of Chemistry Laura Kiessling and Y. Eva Tan Professor of Neurotechnology Ed Boyden, a member of several departments and institutes including BCS and Biological Engineering, will map changes in the sugars' location and structure in healthy and diseased brains, determine how their protein binding changes, and test their interactions in cells to reveal how these sugars influence AD.

ABI project leaders: Top row (l. to r.): Joe Coughlin, Giovanni Traverso, Pattie Maes. Bottom row (l.to r.): Bin Zhang, Laura Kiessling and Edward Boyden. *Images from various sources including Justin Knight.*

Major support for the grants came from the generosity of Kathleen CE '77, SM '77, PhD '86 and Miguel Octavio; the Kojabashian Foundation; David Emmes SM '76; the Marc Haas Foundation; James D. Cook '74 and Christine Cook; Shirley M. Sontheimer '37; the Zoltan Sorell Memorial Fund; Catherine Nyarady '93 and Gabriel Riopel '96; Akiko '99 and Charles Firneno; and the family of Priscilla King Gray and former MIT President Dr. Paul E. Gray '54, SM '55, ScD '60, (Virginia and Tom Army, Amy and Dave Sluyter, Andrew and Yuki Gray, Weezie and Tim Huyck, and all their children) with additional funding from many annual fund donors to the Aging Brain Initiative Fund.

# Different anesthetics, same result: **unconsciousness** by shifting brainwave phase

At the level of molecules and cells, ketamine and dexmedetomidine work very differently, but in the operating room they do the same exact thing: anesthetize the patient. By demonstrating how these distinct drugs achieve the same result, a new study in animals by Picower Institute neuroscientists identifies a potential signature of unconsciousness that is readily measurable to improve anesthesiology care.

What the two drugs have in common, the researchers discovered, is the way they push around brain waves, which are produced by the collective electrical activity of neurons. When brain waves are in phase, meaning the peaks and valleys of the waves are aligned, local groups of neurons in the brain's cortex can share information to produce conscious cognitive functions such as attention, perception and reasoning, said Picower Professor Earl K. Miller, senior author of the new study in *Cell Reports*. When brain waves fall out of phase, local communications, and therefore functions, fall apart, producing unconsciousness.

The finding, led by graduate student Alexandra Bardon, not only adds to scientists' understanding of the dividing line between consciousness and unconsciousness, Miller said, but also could provide a common new measure for anesthesiologists who use a variety of different anesthetics to maintain patients on the proper side of that line during surgery.

"If you look at the way phase is shifted in our recordings, you can barely tell which drug it was," Miller said. "That's valuable for medical practice. Plus, if unconsciousness has a universal signature, it could also reveal the mechanisms that generate consciousness."

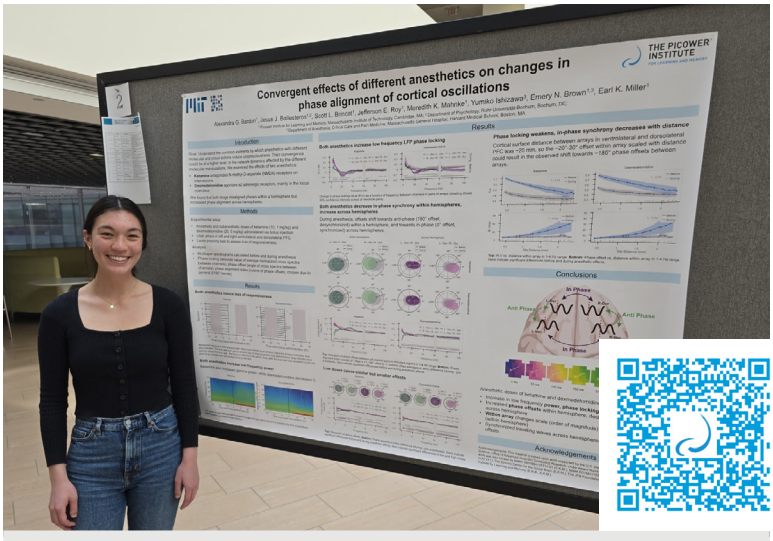
If more anesthetic drugs are also shown to affect phase in the same way, then anesthesiologists might be able to use brain wave phase alignment as a reliable marker of unconsciousness as they titrate doses of anesthetic drugs, Miller said, regardless of which particular mix of drugs they are using. That insight could aid efforts to build closed-loop systems that can aid anesthesiologists by constantly adjusting drug dose based on brain wave measurements of the patient's unconsciousness.

Miller has been collaborating with study co-author Emery N. Brown, an anesthesiologist and Edward Hood Taplin Professor of Computational Neuroscience and Medical Engineering, on building such a system. In a recent clinical trial with colleagues in Japan, Brown demonstrated that monitoring brain wave power signals using EEG enabled an anesthesiologist to use much less sevoflurane during surgery with young children. The reduced doses proved safe and were associated with many improved clinical outcomes including a reduced incidence of post-operative delirium.

Neuroscientists studying anesthesia have rarely paid attention to phase, but in the new study, the team made a point of it as they anesthetized two animals.

After the animals lost consciousness, the measurements indicated a substantial increase in "phase locking," especially at low frequencies. Phase locking means that the relative differences in phase remained stable. But what caught the researchers' attention were the differences that became locked in: Within each hemisphere, regardless of which anesthetic they used, brain wave phase became misaligned between the dorsolateral and ventrolateral regions of the prefrontal cortex.

Surprisingly, brain wave phase across hemispheres became more aligned, not less. But Miller notes that case is still a big shift from the conscious state, in which brain hemispheres are typically not aligned well, so the finding is a further indication that major changes of phase alignment, albeit in different ways at different distances, are a correlate of unconsciousness compared to wakefulness.




Lead author Alexandra Bardon presents a poster of the research. Read a profile of her online by scanning the code.

Distance proved to be a major factor in determining the change in phase alignment. Even across the 2.5 millimeters of a single electrode array, low-frequency waves moved 20-30 degrees out of alignment. Across the 20 or so millimeters between arrays in the upper (dorsolateral) and lower (ventrolateral) regions within a hemisphere, that would mean a roughly 180-degree shift in phase alignment which is a complete offset of the waves.

The dependence on distance is consistent with the idea of waves traveling across the cortex, Miller said. Indeed, in a 2022 study, Miller and Brown's labs showed that the anesthetic propofol induced a powerful low-frequency traveling wave that swept straight across the cortex, overwhelming higher-frequency straight and rotating waves.

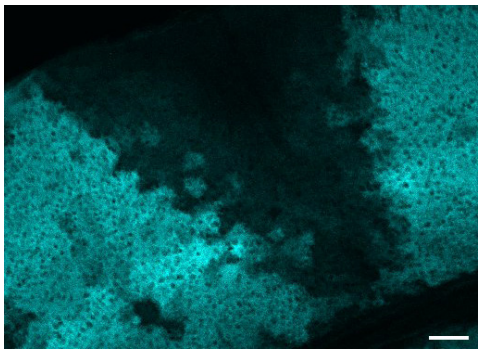
The new results raise many opportunities for follow-up studies, Miller said. Does propofol (another anesthetic) also produce this signature of changed phase alignment? What role do traveling waves play in the phenomenon? And given that sleep is also characterized by increased power in slow wave frequencies, but is definitely not the same state as anesthesia-induced unconsciousness, could phase alignment explain the difference?

# Non-neural brain cells key for processing vision

Astrocyte cells are as abundant in the brain as neurons but have been studied much less. Now research at The Picower Institute shows that they maintain the chemical conditions necessary for groups of neurons to team up to encode information.

The study showed that when researchers knocked out the ability of astrocytes in the visual cortex of mice to produce a protein called "GABA transporter 3 (Gat3)," neurons there became less able as a group to represent information about the movies lab mice were seeing. GABA is a common inhibitory neurotransmitter that sharpens neural activity and astrocytes uniquely use Gat3 to regulate the ambient level of GABA in their area. In the study in *eLife*, knocking out Gat3 in the visual cortex left neurons stewing in a soup of excess GABA that only produced subtle effects on individual neurons, but nevertheless added up to a significant impairment of their efforts as an ensemble responsible for visual function.

"Even if the changes at the level of a single neuron representing a visual stimulus do not change significantly, if a hundred neurons have some small changes, that could add up at the population level to a measurable, significant change," said Newton Professor and senior author Mriganka Sur. Notably, the authors wrote in *eLife*, this is the first study in live mice of Gat3 at scales spanning individual cells and functional ensembles of hundreds of them.



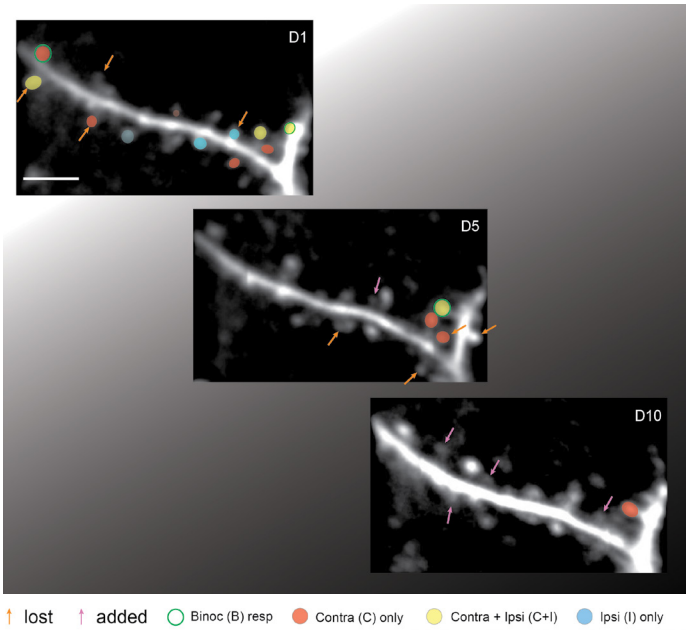
An image from the research shows where scientists knocked out Gat3 expression (stained cyan) in the visual cortex of mice. *Image by Jiho Park.*

To make the discovery, BCS graduate student Jiho Park used a novel implementation of CRISPR/Cas9 gene editing to knock out Gat3 combined with statistical and computational analyses of neural activity at the population level, Sur said. Sur's lab developed the editing tool after receiving an NIH grant back in 2019.

The finding that a lack of Gat3 disrupts neural coordination at the population level might help explain clinical observations that Gat3 reduction in the thalamus increases seizure risk, Gat3 increase in the striatum contribute to repetitive behaviors, and Gat3 reduction in the globus pallidus impairs motor coordination, Park said.

# Extensive rewiring builds binocular vision

The brain's visual system isn't fully hardwired from the start—it becomes refined by what babies see—but the authors of a new study still weren't prepared for the degree of rewiring they observed when they took a first-ever look at the process in mice as it happened in real-time.




An edited research figure shows the same section of neural dendrite at days 1, 5 and 10 of imaging. Arrows indicate spines that will be lost by the next imaging day, or that were added by that day. Circle colors indicate which eye(s) the input came from.

As The Picower Institute researchers tracked hundreds of "spine" structures housing individual network connections, or "synapses," on the dendrite branches of neurons in the visual cortex over 10 days, they saw that refining binocular vision (integrating input from both eyes) required numerous additions and removals of spines along the dendrites to establish an eventual set of connections.

Former graduate student Katya Tsimring led the study in *Nature Communications*, which the team said is the first to track the same connections all the way through the "critical period," when binocular vision becomes refined.

"What Katya was able to do is to image the same dendrites on the same neurons repeatedly over 10 days in the same live mouse through a critical period of development, to ask what happens to the synapses or spines on them," said Newton Professor and senior author Mriganka Sur. "We were surprised by how much change there is."

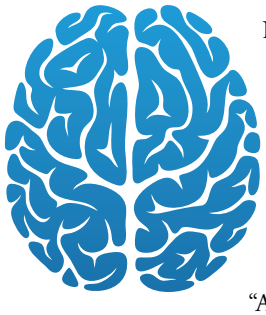
The researchers saw that 32 percent of the spines evident on day 1 were gone by day 5, and that 24 percent of the spines apparent on day 5 had been added since day 1. The period between day 5 and day 10 showed similar turnover: 27 percent were eliminated but 24 percent were added. Overall, only 40 percent of the spines seen on day 1 were still there on day 10.

The scientists asked what entitled some spines to survive.

As the data accumulated, they saw that spines were more likely to endure if a) they were more active, and b) they responded to the same orientation of lines within the images mice viewed as the ones the neuron was tuned to overall. Moreover, across the 10 days, clusters emerged along the dendrites in which neighboring spines were increasingly likely to be active at the same time.

# Review explains brain's division of vision across hemispheres

People have a lot of misconceptions about what the brain's left and right hemispheres do, but one well-known aspect of this division may be even more true than people realize: The brain not only splits up visual spatial perception—processing what's on our left in the right hemisphere and what's on our right in the left hemisphere—it takes cognitive advantage of that. A new review by MIT neuroscientists explains what the field has learned about this division of labor, the trade-off it involves and how the brain ultimately bridges the divide.



"People hear all these myths about the left brain being more analytical and the right brain being more artistic, or people being right-brained vs left-brained. Ninety-nine percent of that is nonsense," said Picower Professor and co-author Earl K. Miller, who co-authored the new review in the journal *Neuropsychologia* with Picower Institute research scientist Scott Brincat. "You think with your whole brain."

But when it comes to visual spatial perception, the brain has evolved separate neural resources for the right vs. left sides of gaze even in later stages of cognitive processing, Miller said. Why? To optimize its capacity.

Studies have shown that even in the prefrontal cortex neural encoding of information about where an object is still is biased toward the "contralateral" hemisphere, or the hemisphere opposite of where the object appears in the field of view. Moreover, research shows that people and animals can remember more things if their presentation is split between hemispheres rather than presented all on one side. Neuroscientists call this the "bilateral advantage."

Notably, the studies that Brincat and Miller review in the new paper show that the split between hemispheres applies only to spatial information—the where something is. Other features like color or shape are processed by both hemispheres.

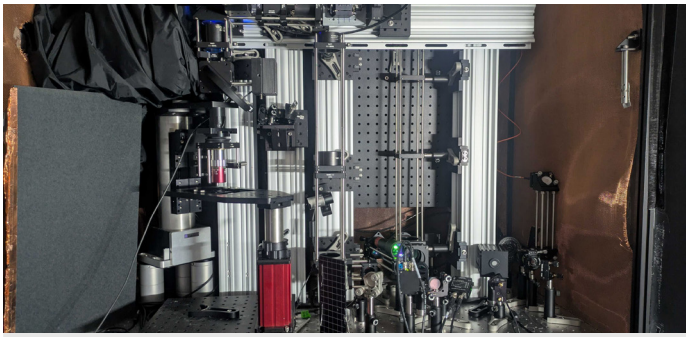
So how does the brain provide us a seamless, unified experience of vision when each hemisphere does its own processing?

"As a tracked target approaches the visual midline, the hemisphere about to receive the target shows a ramp-up of activity well before the crossing time, as if it is anticipating the target," the authors wrote. "Further, activity in the sending hemisphere remains high well after the crossing. Thus, for up to a second or more, neural signals reflecting the target are shared across both hemispheres."

# Imaging tech looks deep into living brain tissue with single-cell resolution

In a new study, an MIT team demonstrates a new microscope system capable of peering exceptionally deep into brain tissues to detect the molecular activity of individual cells by using sound.

"The major advance here is to enable us to image deeper at single-cell resolution," said Newton Professor Mriganka Sur, a corresponding author along with mechanical engineering Professor Peter So and principal research scientist Brian Anthony.



A picture of the microscope system. Image by Tatsuya Osaki.

In the journal *Light: Science and Applications*, the team demonstrates that they could detect NAD(P)H, a molecule tightly associated with cell metabolism in general and electrical activity in neurons in particular, all the way through samples such as a 1.1 mm "cerebral organoid," a 3D mini brain-like tissue generated from human stem cells, and a 0.7 mm thick slice of mouse brain tissue.

In fact, said co-lead author and mechanical engineering postdoc W. David Lee, who conceived the microscope's innovative design, the system could have peered far deeper but the test samples weren't big enough to demonstrate that.

"That's when we hit the glass on the other side," he said.

Still, a depth of 1.1 mm is more than five times deeper than other microscope technologies can resolve NAD(P)H within dense brain tissue. It uses "three-photon" light to stimulate molecules deep in tissue and then photoacoustic detection of the resulting sound waves. No special chemical labels are needed.

"We integrated all these cutting-edge techniques into one process to establish this 'Multiphoton-In and Acoustic-Out' platform," said co-lead author Tatsuya Osaki, a Picower Institute research scientist in Sur's lab.

Lee and Osaki combined with research scientist Xiang Zhang and postdoc Rebecca Zubajlo to lead the study. With the concept of label free, multiphoton, photoacoustic microscopy established in the paper, the team is now looking ahead to further advancing the technology for use in live animals and eventually in clinical applications. In the brain, levels of the molecule are known to vary in conditions such as Alzheimer's disease, Rett syndrome, and seizures, making it a potentially valuable biomarker.

The authors also note that their photoacoustic method could detect other molecules such as the genetically encoded calcium indicator GCaMP, that neuroscientists use to signal neural electrical activity.

# How an MIT professor introduced hundreds of thousands of students to neuroscience

From the very beginning, Mark Bear's philosophy for the textbook "Neuroscience: Exploring the Brain" was to provide an accessible and exciting introduction to the field while still giving undergraduates a rigorous scientific foundation. Since its first print printing in 1995, the treasured 975-page tome has gone on to become the leading introductory neuroscience textbook, reaching students at hundreds of universities and in multiple languages.

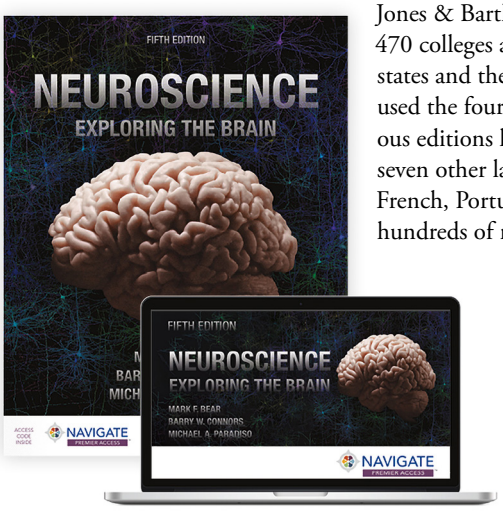
"We strive to present the hard science without making the science hard," said Bear, Picower Professor. The 5th edition of the book, published by Jones & Bartlett Learning, hit stores in July.

Bear said the book instills students with the state of knowledge in the field without assuming prior sophistication in science. When he first started writing the book in the late 1980s (an effort soon joined by his co-authors and former Brown University colleagues Barry Connors and Michael Paradiso) there simply were no undergraduate neuroscience textbooks.

Because universities were only beginning to launch neuroscience classes and majors at the time, Bear recalls that it was hard to find a publisher. The demand was just too uncertain. With an unsure market, Bear said, the original publisher Williams & Wilkins wanted to keep costs down by printing only in black and white. But Bear and his co-authors insisted on color. Consistent with their philosophy for the book, they wanted students, even before they began reading, to be able to learn from attractive, high-quality illustrations.

"Rather than those that speak a thousand words, we wanted to create illustrations that each make a single point." Bear said. "We don't want to overwhelm students with a bunch of detail. If people want to know what's in our book, just look at the pictures."

Another signature of the book throughout its 30-year-history has been the way it presents the process of discovery alongside the discoveries themselves, Bear said. While it's instructive to provide students with the experimental evidence that supports the concepts they are learning, it would bog down the text to delineate the details of every experiment. Instead, Bear, Connors and Paradiso have chosen to highlight the process of discovery via one-page guest essays by prominent neuroscientists who share their discovery stories personally. Each edition has featured about 25 such "Path of Discovery" essays, so more than 100 scientists have participated, including several Nobel prize winners. Among those is The Picower Institute's founding director Susumu Tonegawa. The new edition includes Path of Discovery essays by current Picower Institute director Li-Huei Tsai and Picower Institute colleague Emery N. Brown.




Jones & Bartlett reports that more than 470 colleges and universities in 48 U.S. states and the District of Columbia have used the fourth edition of the book. Various editions have also been translated into seven other languages including Chinese, French, Portuguese and Spanish. There are hundreds of reviews on Amazon.com with an average around 4.6 stars. One reviewer wrote about the fourth edition: "I never knew it was possible to love a textbook before!"

The reviews sometimes go beyond mere internet postings. Once, after Bear received an award in Brazil, he found himself swarmed at the podium by scores of students eager for him to sign their copies of the book. And earlier this year when Bear needed surgery, the anesthesiologist was excited to meet him.

"The anesthesiologist was like, 'Are you the Mark Bear who wrote the textbook?' and she was so excited, because she said, 'This book changed my life'," Bear recalled. "After I recovered, she showed up in the ICU for me to sign it. All of us authors have had this experience that there are people whose lives we've touched."

# Congratulations Myriam and Kwanghun!

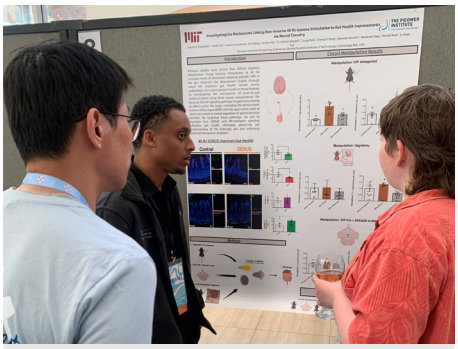
**Myriam Heiman and Kwanghun Chung have each been promoted to the rank of full Professor.**

As of July 1, Picower Institute investigator Myriam Heiman is the John and Dorothy Wilson Professor and Picower Institute investigator Kwanghun Chung has been named the Eugene McDermott Professor in the Brain Sciences and Human Behavior. Congratulations to both on their promotions!

# Retreat sets scene for science sharing

Hundreds of scientists, students and staff from The Picower Institute, the Department of Brain and Cognitive Sciences and the McGovern Institute for Brain Research gathered in Newport June 2-3 for a retreat. Amid the fresh perspective of being surrounded by sun and surf, attendees could hear faculty research talks, including from Menicon Professor Troy Littleton, and exchange ideas at a poster session, a "speed pitching" event, and in small group discussions. All that still left plenty of time for fun and socializing, too, which provide a less formal route to collaboration. The Picower Institute extends many thanks to Wendy Fisher and siblings, whose 2008 gift in honor of their parents, Dana and Betty Fisher, helps to make Picower retreats possible every year. *Photos by Asha Bhakar and Nina Thirakoune.*

Menicon Professor Troy Littleton delivers a research talk



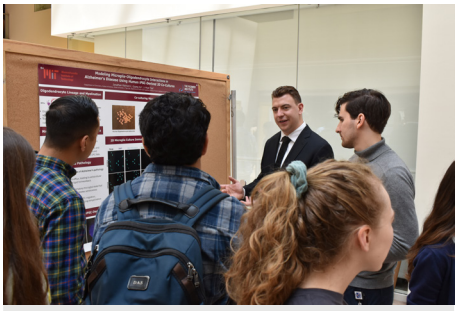
Tsai Lab postbacc Daniel Egziabher presents his research

Retreat attendees engage in a breakout group discussion

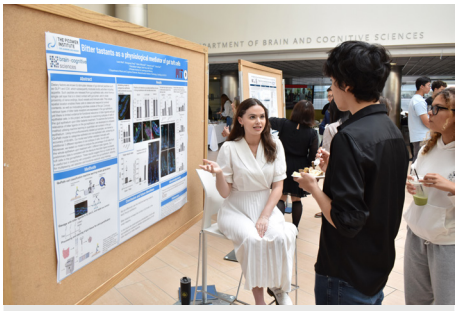
## MSRP

For 10 weeks this summer seven undergraduates from non-research-intensive universities gained exposure and experience to neuroscience in Picower Institute labs as part of MIT's MSRP-Bio program. The students work side-by-side with graduate students and postdocs and then present their work. In all, 102 MSRP-Bio students have worked in Picower Institute labs since 2003. Of those, 93 completed their undergraduate studies and 47 went on to enroll in PhD programs including 10 at MIT and many more at other schools such as Cornell, Yale, Stanford, Princeton and Johns Hopkins. Another 11 have gone to medical school, and 11 others enrolled in MD/PhD programs. Three have earned master's degrees. The rest are either still undergrads, or have taken jobs.

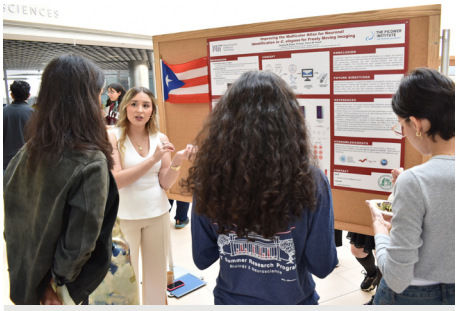
**Scan the barcode** to read an online feature about participants Jonathan Palmiero and Laura Neal.



Jonathan Palmiero of Marist University presents Alzheimer's-related research he conducted using induced pluripotent stem cell cultures in the lab of Professor Li-Huei Tsai.



Laura Neal of Macalester College explains her research in the lab of Associate Professor Gloria Choi on imaging intestinal cells that might influence eating behavior and mood.



Carolina Rivera-Mendez of the University of Puerto Rico-Mayaguez shows her work in the lab of Associate Professor Steven Flavell in which she analyzed a technology that enables individual imaging of a lab animal's neurons.

**Congratulations new PhDs!** Two more graduate students have earned PhDs in Picower Institute labs this summer.

**Dr. Leyla Akay**, Tsai Lab, "When Memory Unravels: How the Alzheimer's disease risk gene APOE4 impacts oligodendrocyte metabolism and myelination"

**Dr. Djuna von Maydell**, Tsai Lab, "Mechanisms of genetic risk in Alzheimer's disease"

# Many Mechanisms of Mood

*Picower Institute studies reveal a number of ways moods emerge in the brain and therefore many potential paths to address depression, PTSD, anxiety and bipolar disorder.*

In illustrator Yi Zheng's conception reflecting the research of Professor Susumu Tonegawa, the amygdala supplies the "paint" needed to obscure a fearful mood with a more rewarding and joyous one.

Daily life is all we need to sense that many factors influence our feelings, but the job of neuroscientists is to go beyond intuition with rigorous, experimental observation. That's how they advance understanding. Via novel investigations of a variety of brain mechanisms that influence mood, several Picower Institute labs are advancing new ideas with the potential to address PTSD, anxiety, depression and bipolar disorder.

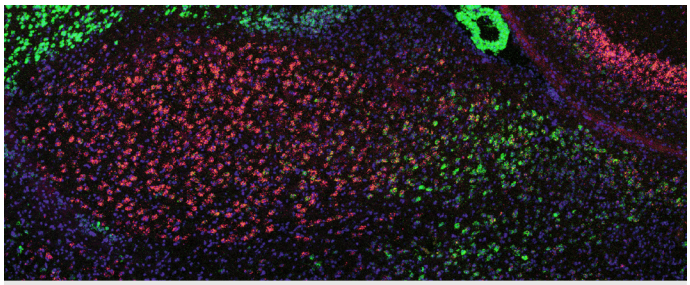
They are aware of the stakes. In the U.S., nearly 10 percent of adults experience a mood disorder in any given year, according to the National Institute of Mental Health. The need for better therapeutics and diagnostics is widespread and urgent.

For instance, in research stretching from 2014 to this year, Picower Professor Susumu Tonegawa has pinpointed exact brain circuits that associate the memory of an experience with a feeling about it. When his lab demonstrated in mice how that mechanism could be manipulated to change a negative feeling about a memory into a positive one, messages from people with anxiety disorders came flooding in, recalls longtime lab research scientist Michele Pignatelli. Never mind that the manipulation required genetically engineering the mice so that their neurons could be controlled by light from a fiber optic cable. People expressed eagerness to have fiber optics implanted in their brain.

The poignant pleas illustrated how pervasive and terrible disorders of mood can be. Tonegawa said he hopes his fundamental insights will find clinical application, and with the same motivation, three other Picower labs—those of Gloria Choi, Emery N. Brown and Elly Nedivi—are also studying novel mechanisms of mood.

## Antagonism in the amygdala

Tonegawa's research, pioneered in the lab by former graduate student Joshua Kim, centered on the amygdala brain region. Though the amygdala had already been established as a locus for emotion, his lab's studies were the first to reveal both precisely and causally, at the molecular, cellular and circuit level, how the brain endows memories with emotional associations.



The almond-shaped basolateral amygdala region in the center of this image features distinct populations of cells: On the left are red-stained, negative valence Rspo2-expressing cells, and on the right are green-stained, positive valence Ppp1r1b-expressing cells. *Image by Tonegawa Lab.*

Kim and fellow lab member Roger Redondo set the table for lab's line of research with a 2014 study that took advantage of their recently perfected method for identifying the exact ensemble, or "engram," of cells that encode a specific memory. Upon pinpointing engram cells, the scientists could then genetically engineer them with an emerging technology called optogenetics to make them controllable with light. Tonegawa's team thereby gained the ability to take control of memories. In the study, Redondo and Kim labeled engrams in the brain's hippocampus, which encodes memories of places, and the "basolateral" area of the amygdala (BLA) while exposing male mice to something like a modern-day twist on how Pavlov associated a conditioned stimulus (the sound of a bell) with an unconditioned one (a food reward). In Tonegawa's case, the conditioned stimulus was a place and the unconditioned stimulus was either a harmless but annoying shock or the company of a female mouse. The mice naturally associated the place memory with a good or bad feeling depending on the unconditioned stimulus and behaved accordingly when the researchers used their optogenetic control to reactivate the place memory. But then, the team reactivated the engram in the hippocampus while exposing the mice to the opposite unconditioned

stimulus. When they did so, they successfully flipped the feelings the mice displayed for the place memory. And in the brains of the mice, the researchers could see that the place memory was now connecting with different cells in the amygdala than before.

The research team realized that the BLA not only endowed memories with their valence of good or bad feeling, but also that potentially different populations of cells in the region were responsible. To investigate that hypothesis, Kim led a new study in 2016. With Pignatelli and other members of Tonegawa's lab, Kim employed clever molecular techniques to discover that the BLA contained two spatially separated populations of cells with distinct markers of gene expression and opposite functions. In the region's posterior, cells that uniquely expressed the protein Ppp1r1b encoded positive valence, and cells in the anterior that uniquely expressed Rspo encoded negative valence. The study showed that these populations drove behavior. For instance, mice would show attraction to a place when posterior cells were optogenetically activated and aversion to a place when anterior cells were activated. Moreover, Kim discovered that the two BLA populations were locked in a circuit of mutual inhibition. Engaging one group suppressed the other. For example, mice exposed to a shock wouldn't show as much fear if their posterior BLA cells were optogenetically activated because those cells would compete with the activity of the anterior cells that encoded fear of the shock.

That antagonism played out in a 2020 study in which Kim and graduate student Xiangyu Zhang tracked how the different populations battled during "fear extinction," in which mice originally shocked in a place were later returned with no further shocks, ending the fear. Rspo2 cells were more active when the fear was learned and Ppp1r1b cells were more active during the fear extinction. Moreover, optogenetically activating Ppp1r1b cells accelerated fear extinction and suppressing the neurons made fear extinction harder, demonstrating that Ppp1r1b cell activity suppresses the valence encoded by Rspo2 cells.

"This phenomenon of fear extinction, it turns out, is not just the subsiding of an acquired fear memory," Tonegawa said. "There is an active process, an active mechanism, to counter and abolish fears. Under some conditions this fear extinction becomes very ineffective and that's where we see a connection to post-traumatic stress disorder."

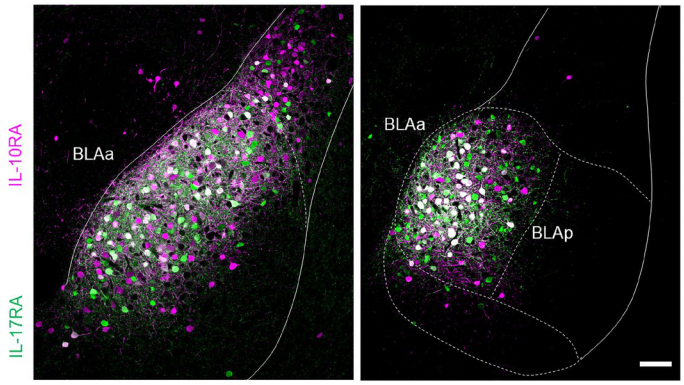
The study also showed that the Ppp1r1b cells are the same neurons that encode the sense of reward, explaining why it feels so joyous when an expected fear doesn't materialize (Tonegawa cites the elation students feel when a dreaded exam is canceled).

This past April the lab answered another key question about this mechanism of mood and memory: What triggers it? Dopamine is known for signaling reward, and in the new study Zhang, former graduate student Kaetlyn Flick and Pignatelli rigorously proved that dopamine from the brain's ventral tegmental area specifically cued each BLA population to assign negative valence to fear memories and positive valence to fear extinction memories.

In all, the lab has not only shown which BLA cells assign valence, but also that specific dopamine delivery circuits instigate that action, providing a molecular roadmap toward treatments for PTSD or anxiety.

## Immune influence

Also in April, Associate Professor Gloria Choi's lab published a study identifying an entirely different mechanism of mood—the immune system—that acts on the same Rspo-expressing population that Tonegawa characterized.




Two views of the basolateral amygdala show that only cells in the anterior region (BLAa) harbor receptors for inflammatory IL-17 immune molecules (green) and anti-inflammatory IL-10 molecules (magenta). *Image by Byeongjun Lee.*

Before Choi began the study with collaborators at Harvard, doctors had observed that some people taking a psoriasis medication that suppresses the immune system had experienced severely negative thoughts. The medicine worked by blocking the "IL-17RA" receptor for inflammatory signaling molecules including IL-17C. Choi's study, in mice, explained how that resulted in psychiatric symptoms. Blocking the receptor in the body left an excess of IL-17C to find its way to the brain. When IL-17C reaches the BLA, the study showed, receptors on Rspo neurons soaked in the molecule, activating the cells and producing anxious behaviors in the mice.

The study, co-led by postdoc Byeongjun Lee and former postdoc Jeong-Tae Kwon also found that the cells have receptors for an anti-inflammatory molecule, IL-10. When they blocked a receptor of IL-10 on the anterior BLA neurons, the mice acted more anxiously, suggesting that IL-10 normally helps to keep anxiety in check.

Choi marvels at how the molecules' opposing effects on the immune system (triggering inflammation or calming it) are mirrored in the amygdala.

"To have that system exactly reflected in the brain and to have the same population expressing these two different kinds of receptors so that when they are engaged they have opposite effects, I think, is so amazing and so beautiful," Choi said. "It really is canonical evidence that these two systems, the brain and the immune, have evolved together to talk to each other."

Why should they? We often withdraw and hunker down when we don't feel well. That's probably not just because of fatigue, Choi said. A little anxiety when we are unwell might protect us, perhaps by encouraging us to conserve energy and avoid danger in our weakened state. It also protects the community by reducing our desire to go near others. In fact, when we are sick, Choi said, the blood-brain barrier that normally filters what gets to the brain opens up potentially to facilitate this messaging from the peripheral immune system to the central nervous system.

Choi's study raises key clinical questions. Should drug makers be more wary that manipulating the immune system in the body might inadvertently manipulate the brain? And can the immune system be intentionally manipulated to treat mental health disorders? The key to both questions might be developing better ways to ensure that therapies only act where they are supposed to, Choi said.

*(Continued on next page)*

"How do you target the brain but not the body and how can you target the body but not the brain?" Choi said. "That really is the homework for the pharmaceutical industry."

## Disrupting dynamics

Choi and Tonegawa acknowledge that there is more to the mechanisms they are studying, and to mood disorders in general. The brain is a complex network of networks linked both by direct neural connections and the flow of neuromodulatory chemicals.

For instance, in a review paper published in February, Edward Hood Taplin Professor Emery N. Brown and co-authors noted three broad-based theories of depression as they explained why eight different anesthetic drugs might be effective antidepressants (so far only ketamine is used that way).

One theory holds that depression arises from perturbations of brain networks that normally collaborate to regulate emotion and balance attention to internal thought vs. external stimuli. Another theory focuses on a deficit of BDNF, a brain chemical that promotes increased connectivity among neurons. Yet another theory focuses on the inhibitory neurotransmitter GABA, suggesting that reduced levels can promote depression when neurons become overexcited.

After noting that many different anesthetic drugs have been experimentally (and anecdotally) observed to relieve depression, Brown's review describes how drugs including ketamine, propofol, and dexmedetomidine directly intersect with the mechanisms underlying these theories. Ketamine increases BDNF and alters network connectivity. Propofol works by increasing GABA and it both increases BDNF and alters broader network connectivity. Dexmedetomidine also increases BDNF and reduces broad network connectivity.

"The common factor among all the anesthetics is that they change brain dynamics," the review states. "We propose that that the therapeutic actions of anesthetics in treating major depressive disorder or treatment-resistant depression could be their capacity to disrupt and help rewire brain networks."

Many details remain to be discovered. Brown takes inspiration from an old but nonetheless effective way of disrupting intractably depressed brain networks: electroconvulsive, or "shock," therapy (ECT). On the way to understanding whether and how different anesthetics might do a better job and cause fewer cognitive side effects, Brown's lab led by postdoctoral Picower Fellow Macauley Breault and senior postdoctoral associate Sirma Orguc are now gathering data from ECT patients at McLean Hospital near Boston. They'll seek to determine a more detailed understanding of how ECT and the different anesthetics given to patients during the procedure combine to alter brain networks.

"What we'd like to do is at least have some idea what the comparator (ECT) is doing," Brown said. "If we do a clinical trial where one group gets anesthesia alone and the other group gets ECT, then at least we'll have some idea of what we should be looking for."

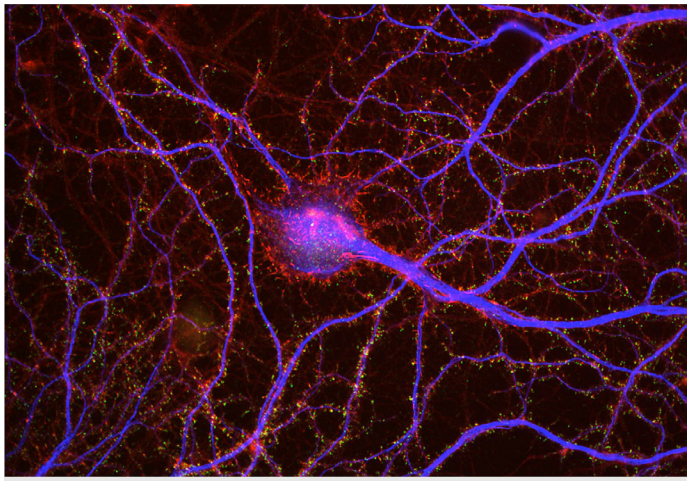
## A lead on bipolar disorder

William and Linda Young Professor Elly Nedivi is on the trail of another mechanism of mood: genetic risk for bipolar disorder.

In 2019 Nedivi's lab, led by former postdoc Mette Rathje, published a study showing that people diagnosed with bipolar disorder had lower levels in the brain of the CPG2 protein, a product of the SYNE1 gene which had been established as a genetic hit for bipolar disorder. They then identified specific patient mutations (or combinations of them) in the part of SYNE1 controlling CPG2 expression and showed that they led to reduced expression of CPG2.

The study raised the possibility that testing people for particular mutations of SYNE1 could be a biomarker of bipolar disorder risk. Such an objective marker could help increase confidence when diagnosing bipolar, Nedivi said. Misdiagnosis can lead to patients receiving inappropriate treatment, sometimes for years.

"The diagnostic is entirely subjective through symptoms," Nedivi said. "But there is a lot of overlap between bipolar symptoms and either schizophrenia or major depression. So when patients come to a doctor, depending on what symptoms they have at the time, the diagnosis is not always simple. Having an objective biological diagnostic would make the whole treatment journey potentially a little less fraught"



Elly Nedivi's lab has linked low levels of the protein CPG2 to increaed risk of bipolar disorder. Here they've stained neurons to highlight the protein (yellow/green) along the spines of the cells' dendrite branches.

Nedivi originally discovered CPG2 decades ago as part of fundamental studies of how neurons forge and edit their circuit connections, or "synapses," to enable the brain to flexibly respond to experience, a phenomenon known as "plasticity." CPG2 does this by regulating the number of receptors for the neurotransmitter glutamate at excitatory synapses. This doesn't immediately explain why a deficit could increase bipolar risk, but it does provide some clues. Like BDNF, CPG2 affects neural connectivity and its expression depends on neural activity, Nedivi said. CPG2's effects on the refinement of neural circuits also kicks in very late in brain development (i.e. adolescence), when bipolar onset often occurs. And finally, CPG2 expression is more prominent in areas of the brain related to cognition.

Since the 2019 study, the lab led by postdoctoral Picower Fellow Baovi Vo has been working to further bolster the evidence base for which particular SYNE1 mutations most contribute to CPG2 expression anomalies. To do that they are digging deep into databases of human cell cultures derived from thousands of people. That effort will vastly increase the lab's sample size, increasing the reliability of potential genetic biomarkers.

From sources as diverse as memory, immune activity, anesthesia and synaptic plasticity genes, many mechanisms converge on mood. Those Picower Institute insights can inform new ways to improve mental health.

# Upcoming EVENTS

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

## Circuits of Survival and Homeostasis

**Tuesday, October 21, 2025**
MIT Building 46
Singleton Auditorium (46-3002)
Hosted by Sara Prescott, PhD

THE PICOWER INSTITUTE FOR LEARNING AND MEMORY

| | |
|---|---|
| 9:30-9:45am | Opening Remarks |
| 9:45-10:30am | **Cliff Saper,** Harvard University |
| 10:30-11:15am | **Qin Liu**, Washington University in St. Louis |
| 11:15am-12:00pm | **Mark Krasnow**, Stanford University |
| 12:00-1:00pm | Lunch |
| 1:00-1:45pm | **Li Ye,** Scripps Research Institute, HHMI |
| 1:45-2:30pm | **Zachary Knight,** UC, San Francisco, HHMI |
| 2:30-2:45pm | Break |
| 2:45- 3:30pm | **Yuki Oka**, Caltech |
| 3:30-4:15pm | **Ya-Chieh Hsu,** Harvard University |
| 4:15-4:30pm | Closing Remarks |

Save the Date:
May 19, 2026

## The Neuroscience of Democracy

THE PICOWER INSTITUTE FOR LEARNING AND MEMORY

Freedom Together Foundation

A joint symposium of
The Picower Institute
for Learning and Memory
and The Freedom Together Foundation

MIT Building 46, Singleton Auditorium

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## OUR VISION

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, behavior, and consciousness. Institute neuroscientists explore the brain and nervous system 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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For more information on our research or how to make a gift to The Picower Institute for Learning and Memory, please contact: Asha Bhakar, PhD, abhakar@mit.edu, Tel: 617-258-0759.

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**TOP ROW:** **Mark F. Bear**, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences; **Emery Brown**, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience, Department of Brain and Cognitive Sciences, Institute of Medical Engineering and Science core faculty; **Gloria Choi**, Associate Professor, Department of Brain and Cognitive Sciences; **Kwanghun Chung**, Eugene McDermott Professor, Departments of Chemical Engineering and Brain and Cognitive Sciences, Institute of Medical Engineering and Science core faculty; **Linlin Fan**, Samuel Goldblith Assistant Professor, Department of Brain and Cognitive Sciences; **Steven Flavell**, HHMI Investigator, Associate Professor, Department of Brain and Cognitive Sciences; **Myriam Heiman**, John and Dorothy Wilson Professor of Neuroscience, Department of Brain and Cognitive Sciences; **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, Departments of Brain and Cognitive Sciences and Biology; **Sara Prescott,** Assistant Professor of Biology; **Mriganka Sur**, Paul E. Newton Professor of Neuroscience, Director of The Simons Center for the Social Brain, Department of Brain and Cognitive Sciences; **Susumu Tonegawa**, Picower Professor of Biology and Neuroscience, Departments of Brain and Cognitive Sciences and Biology, HHMI Investigator, 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; **Brady Weissbourd,** Assistant Professor of Biology; **Matthew Wilson**, Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology, Associate Director, The Picower Institute for Learning and Memory.