

Brain Biomarkers

Picower labs are developing objective, minimally invasive indicators of brain health to improve diagnoses and measures of treatment efficacy. Pg. 8



Neuroscience News



FALL 2026



THE PICOWER
INSTITUTE
FOR LEARNING AND MEMORY



DIRECTOR'S MESSAGE

Dear Friends,

We are proud to bring you the news in this edition—not only word of our latest research but also the appointment of Emery N. Brown as an Institute Professor, MIT's highest faculty honor—but we do so with heavy hearts. As you may already know, our founder Susumu Tonegawa died July 11 at the age of 86. We feel deeply the weight and sorrow of his loss.

Susumu inspired us all. His vision and work brought The Picower Institute into being and so helped enable all the discoveries we have made and the careers we have launched. His pioneering application of molecular biology techniques to the study of memory produced many groundbreaking findings and the world-changing immunology research that preceded it earned the honor of the 1987 Nobel Prize in Physiology or Medicine. You can learn more about his life and work in our reprint of MIT's official obituary on page 6.

More than just his record of accomplishments, Susumu leaves us with many deeply motivating lessons about the pursuit of science.

One is to tackle important questions relentlessly. Susumu realized early on in his career that the emerging science of molecular biology could enable him to address fundamental unsolved biological questions, and he followed that realization with determination, rigor and creativity.

Another is that the complex mysteries of the brain can be solved. When Susumu embarked on his studies of memory, very little was known about its underlying mechanisms. But he brought new tools and built new communities of researchers to tackle the question. As a result of his work, today we know much more, and we are eager for all the future discoveries his work has made possible.

A third lesson is that basic research yields important applications. His findings about memory have potential to advance psychiatric and neurological care. And across this institute, scientists he recruited and mentored have similarly demonstrated that fundamental inquiry leads to new therapeutic strategies.

Susumu also taught us that large advances come from bringing together diverse perspectives. He combined molecular biology with other disciplines to great success. He built this institute to reflect the true breadth of neuroscience, combining labs that study specific genes and proteins with those who study the coordinated activity of millions of cells.

We miss him, but his lessons remain with us.

MYRIAM HEIMAN, DIRECTOR

The Picower Institute for Learning and Memory

Electric fields help guide neural activity

A new study shows that a lot of ongoing fluctuations in the brain's activity can be explained by the influence local electric fields exert on neurons, a phenomenon called “ephaptic coupling.” The finding, published in *Cerebral Cortex*, adds to evidence that the brain's electric fields act as important control signals for underlying brain function.

“The brain is a rollicking sea of electrical influences,” said study co-author Earl K. Miller, Picower Professor of Neuroscience in The Picower Institute. “But the traditional view of brain function focuses only on the spiking and synaptic connections among individual neurons. Now, there is growing evidence for electric field effects. For instance, in this study we show that neural variability is explained by how ephaptic effects are influencing neural activity.”



Neurons are electrical. A new study finds that the fields generated by their synchronized, rhythmic activity can, in turn, influence their activity.

In 2022 and 2023, Miller and fellow author Dimitris Pinotsis, Associate Professor at City St. George's, University of London, published several studies showing that local electric fields in the brain's cortex not only reflected the information neurons were processing better than any individual neuron did, but also that the fields actively helped to organize the underlying neural spiking that executes that processing. Like an orchestra conductor, the electric waves can conduct crowds of neurons so that they are playing the same tune. They further theorize that fields physically exert influence on the structure of the brain via cytoelectric coupling, in which the fields alter the cytoskeleton of neurons, optimizing them to oscillate in synchrony.

Because electric fields can be manipulated, Miller and Pinotsis argue in the new study that understanding how they influence momentary

brain function could open the door to therapeutic interventions designed to improve that when it is faltering in disease. It would be difficult to adjust every neural connection, but ephaptic coupling suggests that intervening at the level of electric fields could accomplish that therapeutic end, the researchers said.

In the duo's prior studies, they analyzed signals averaged over time, documenting that in general, even though local (or “mesoscale”) electric fields in the cortex arise from the electrical activity of individual neurons, the field ultimately represents and coordinates their function. Think of it this way: Neurons are like individual citizens and the electric fields are their government. Once the citizens establish a government with their individual votes, they are then subject to and unified

by the laws the government creates and enforces.

In the new study, the team asked whether mesoscale electric fields not only provide this ephaptic influence overall during working memory tasks, but also trial by trial. After all, that's closer to the timescale of actual brain operations that matter both for healthy function or in disease.

So the scientists looked anew at the data they recorded as animals played a simple video game. Meanwhile, the scientists used electrodes implanted in a region of the cortex to record neural

electrical spiking and more collective local field potentials (LFPs). Using that information, they calculated the local prevailing electric field at each moment.

In their statistical analysis of the data, they made several findings. One, as expected, was that neural activity varied sometimes quite widely trial by trial during the task. Another, using a mathematical technique called Granger Causality, showed that the direction of influence between the electric field and the neural activity was strongly in favor of the field.

Moreover, the team's modeling and calculations showed that the strength of the ephaptic coupling between the field and the neural activity was proportional to the variations in the LFP power—another sign that the fields influenced the neural activity.

Brain circuit keeps tabs on what just happened to aid judgment of **what's happening now**

To judge what's going on around it in a highly variable, fast-paced world, the brain has to be open to whatever new sensory information may come its way yet also try to leverage prior experience to make predictions. In a new study in *Science*, MIT neuroscientists identify a circuit that links a sensory decision-making region with one that advises it on how much sensory information just changed.

"This circuit organizes a comparison between what has just happened versus what is happening now in the sensory world in a manner that can be used to act," said study senior author Mriganka Sur, Newton Professor in The Picower Institute.

Study lead author Ning Leow, a former graduate student in Sur's lab, said the study in mice sheds light on closely analogous circuitry in humans, in which an area of the prefrontal cortex (the anterior cingulate cortex, or ACC) makes sensory decisions. The new study shows it bases those decisions on advice about immediate past history from an area of the thalamus called the pulvinar (in mice, it's called the lateral posterior thalamus, or LP).

"The brain does not evaluate each new event from scratch," Leow said.

Leow and Sur mapped the copious inputs to the LP-ACC circuit in a paper in 2022. That study showed how the circuit seems well positioned to help focus attention, which is what it was known for at the time. Sur and Leow further hypothesized that it might also have a hand in guiding decisions based on sensory information. The new study presents multiple lines of evidence that it does.

The findings not only shed light on a fundamental function of the brain, Sur said, but could also be applicable to studies of autism, in which many patients show significant differences in the predictions they make about the sensory world. Often, this manifests as difficulty filtering out stimuli that neurotypical people are able to regard as recurring and therefore mundane.

To conduct the study, the researchers trained lab mice to play a video game in which dots on a screen would drift around, but at least some would move together in the same direction (left or right). In each trial, the mice had to discern that trend. From one trial to the next, then, the sensory cue could vary not only by the direction of movement, but also by what proportion of dots were participating. For instance, on one trial maybe 64 percent of the dots would move left and on the next

trial maybe 16 percent of the dots would move right. In this way, the researchers could measure a whole continuum of differences from one trial to the next.

Meanwhile, as mice played the game, the scientists used a two-photon microscope to record the activity of the LP-ACC circuit and the response of neurons in the ACC. In some experiments, they used a technique called optogenetics to artificially activate the circuit.

By tracking how mice performed the task trial after trial, the researchers were able to see that the mice indeed factored in not only what they were seeing in the moment but also what they had just seen previously.

To determine if that behavior arose from the LP-ACC circuit, the researchers used optogenetics to perturb it (by stimulating extra

activity in the LP's inputs into the ACC). Doing so proved to disrupt how mice used recent sensory history when evaluating new evidence.

"That showed the pathway is causally involved in the comparison process that influences how current evidence is interpreted rather than merely carrying the information," Leow said.

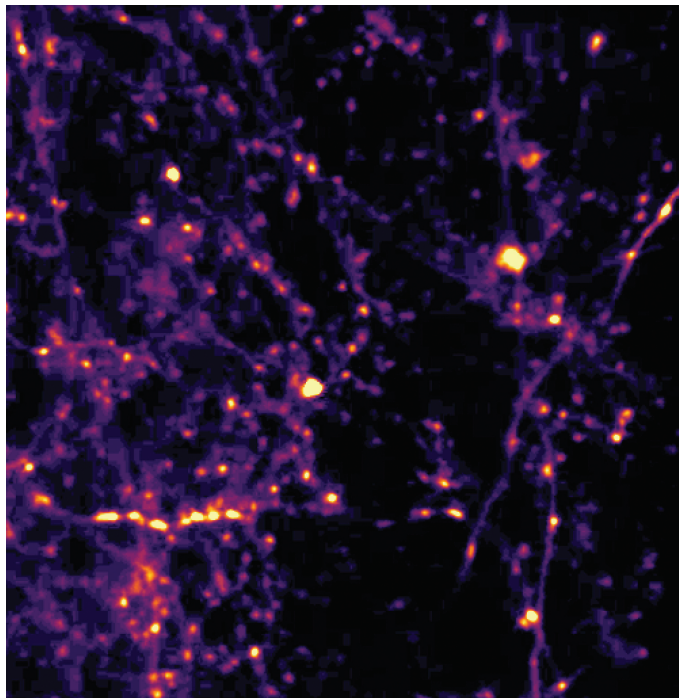
Moreover, using the microscope imaging (which visualizes calcium levels in neurons, a close proxy of the electrical activity), the researchers extensively analyzed the activity patterns of the LP input into the ACC and how ACC neurons reacted to that input.

"The main takeaway is that the LP and ACC were performing different jobs," Leow said. "The pulvinar doesn't appear to be making the decision itself. Instead, it sends that history-referenced sensory comparison to the frontal

cortex. The ACC then transforms that information into the neural activity that predicts the animal's final choice."

Essentially, the pulvinar advises the ACC on the degree of change so that the frontal cortex can consider whether it's time to change a guess. After all, if a mouse is guessing right and little is changing, why not keep on trucking? But if there's a big change, then it might make sense for the mouse to re-evaluate what it's thinking.

It turns out, the brain has this dedicated circuit for doing so.



An edited and colored figure from the research highlights axons from the LP in the ACC. Image courtesy of Ning Leow.

Team to study how Alzheimer's risk varies with hormone replacement

While women affected by symptoms associated with menopause can turn to hormone replacement therapy (HRT), conflicting epidemiological evidence makes it hard to assess whether HRT will increase or decrease their chance of later developing Alzheimer's disease. Nevertheless, current guidelines recommend that HRT start within 10 years of menopause onset or before 60 years of age. With a new Women's Health Initiative Award from the Massachusetts Life Sciences Center, MIT researchers plan a study to discover the mechanisms of molecular and cellular changes by which HRT shapes individual women's Alzheimer's risk.

The goals of the research team, led by Picower Professor Li-Huei Tsai in The Picower Institute for Learning and Memory and Professor Manolis Kellis in the Computer Science and Artificial Intelligence Lab, are to identify risk factors that will help women and their physicians make more informed and personalized decisions and to accelerate the development of therapies that optimize the positive benefits and prevent any adverse effects of HRT in women who may be at risk.

The study will begin with "big data" transcriptomic, epigenomic and metabolomic profiling of 369 women who donated brain tissue samples

post-mortem. The dataset will enable the researchers to gain deep insights into how HRT, when administered, affected the molecular and cellular activity of each woman's brain cells over time and how that varied with individual factors such as genetic background, the timing of HRT (if any), aging, and whether they developed Alzheimer's.

They will also analyze why HRT taken during midlife may have effects that persist in the brain decades later. The researchers hypothesize that hormone exposure creates a lasting molecular memory by reshaping the 3D organization of the genome, changing which genes brain cells can activate or suppress as they age.

As these computational analyses yield specific predictions, the researchers will test them in the lab using advanced 3D brain tissue models called cerebral organoids.

Finally, the team will input their predictions about the underlying molecular processes that mediate HRT's role in protection or promotion of Alzheimer's into AI systems to predict new treatments that support risk mitigation. Then they will test those treatment possibilities in the organoids to identify the most promising ones.

New microscopy tech reveals brainwide activity

MIT engineers have invented a new microscope that can image electrical activity in neurons and circuits distributed across the brain of an entire organism, the experimental model *Danio rerio* (zebrafish).

Using a microscope that they adapted for fast, high-volumetric rate imaging, the researchers were able to track electrical activity across the brain on the scale of milliseconds.

"All of the parts of the brain are connected together, so if you want to truly understand the brain, you have to understand how all the neurons work together as an emergent whole," says Ed Boyden, the Y. Eva Tan Professor in Neurotechnology at MIT; a professor in several MIT

departments and the McGovern Institute for Brain Research; and an affiliate member of The Picower Institute.

Boyden is the senior author of the study in *Nature Methods*. Postdocs Zeguan Wang, of Boyden's Lab, and Jie Zhang, of Picower Institute Professor Matt Wilson's Lab, are the lead authors. Wilson, Sherman Fairchild Professor at MIT, is a co-author.

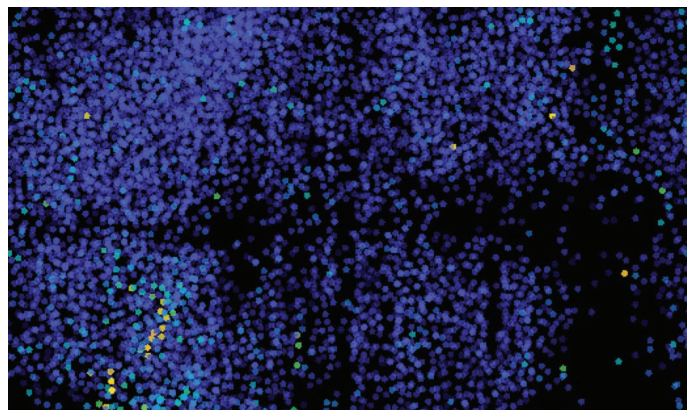
To enable direct imaging of voltage, researchers have developed proteins called genetically encoded voltage indicators (GEVIs). When a neuron fires an impulse, the protein fluoresces, which can be detected with a fluorescence microscope.

"Neurons compute using electrical activity, so with voltage imaging, you can get direct observation of that," Zhang says.

To achieve brainwide imaging using GEVIs, the MIT team modified a commonly used microscope known as a light sheet microscope. The researchers increased the image acquisition speed of the microscope's camera, and they also boosted the scanning speed of the microscope using a technique called remote refocusing.

Using this approach, the researchers showed that they could scan the entire zebrafish brain 200 times per second, or once every five milliseconds.

To test the new microscope, the researchers engineered neurons in larval zebrafish to express a voltage indicator called Positron2-Kv. The researchers imaged the brain as the fish were resting, and they were able to observe single voltage spikes from neurons, as well as rapid bursts of spikes. Additionally, this technique revealed patterns in how the brain is activated following a stimulus such as ultraviolet light.



MIT researchers have developed a method for imaging neuron activity in the zebrafish brain. Each colored spot (green and yellow) represents an active neuron. *Image courtesy of the researchers.*

Emery N. Brown named “Institute Professor”

Emery N. Brown, a physician and neuroscientist who studies how anesthesia affects the brain, is one of three MIT Professors to have been awarded MIT’s highest faculty honor: the title of Institute Professor.

Brown, who has been a member of the MIT faculty since 2005 and a member of The Picower Institute since 2016, says he is “tremendously honored” to be appointed as an Institute Professor.

“It’s a pleasure to know that your colleagues hold you in such high esteem and that the work that you’re doing is valued,” said Brown, the Edward Hood Taplin Professor of Medical Engineering. “When you look down the list of people who have had this title, it’s an amazing group.”

After graduating from Harvard University with a bachelor’s degree in applied mathematics in 1978, Brown earned a PhD in statistics, also from Harvard, and an MD from Harvard Medical School. Until recently he was also a practicing anesthesiologist at Massachusetts General Hospital.

Throughout his career, Brown has made contributions in several different areas of neuroscience. In the early stages of his research, he developed statistical methods to characterize the properties of the human circadian clock. He showed how light exposure can shift the phase of the human clock, depending on the circadian phase during which the light is administered. He also developed methods to demonstrate, from analyses of physiological data collected under special low-light conditions, that the intrinsic period of the human clock, like that of other species, is closer to 24 hours and not 25. Brown also measured the impact of shift work schedules that were designed using circadian physiology.

Later, he developed new statistical techniques and signal processing methods to analyze data collected in systems neuroscience experiments.

As part of this work, he devised algorithms to decode the position of an animal in its environment by reading the activity of a small group of place cell neurons in the animal’s brain.

Joining MIT’s faculty just over 20 years ago represented an “inflection point” in his career, Brown says.

“I was an anesthesiologist doing statistical research, interested in neuroscience, and MIT allowed me to tie all those together,” he says.

Over the past two decades, Brown has applied statistical techniques to studying what happens to the brain under anesthesia. His work has revealed how drugs such as propofol alter the brain’s intrinsic oscillations, which can be seen with electroencephalography (EEG).

During the awake state, these oscillations usually have high frequencies and low amplitudes, but as anesthetic drugs are given, they shift to low frequencies and high amplitudes. These changes disrupt normal communication between different brain regions, leading to loss of consciousness.

Brown has also shown that these EEG oscillations can be used to monitor whether a patient is too deeply unconscious, and he has developed a closed-loop anesthesia delivery system that can monitor these oscillations in real-time and guide anesthetic dosing during surgery.

In January 2025, Brown was presented with the National Medal of Science. Among his other awards, he is also a recipient of a National Institutes of Health Director’s Pioneer Award, the Gruber Prize in Neuroscience, and the Swartz Prize for Computational and Theoretical Neuroscience. He is one of a small group of researchers to be an elected member of all three National Academies (Medicine, Sciences, and Engineering), as well as the National Academy of Inventors.

Honorary degree

On July 22, the University of A Coruña in Galicia, Spain, awarded Picower Institute investigator Emery N. Brown, Edward Hood Taplin Professor of Medical Engineering at MIT, an honorary degree recognizing his research to understand the neuroscience of anesthesia. The university described Brown, who delivered a lecture at the ceremony, as “one of the most prominent figures in international biomedical science, who transformed the understanding of anesthesia, consciousness and the functioning of the human brain.”



Susumu Tonegawa, renowned molecular biologist and Nobel laureate, dies at 86

Tonegawa made landmark discoveries about how the immune system generates antibody diversity and how the brain forms memories.

Susumu Tonegawa, the Picower Professor of Biology and Neuroscience at MIT and a Nobel laureate, died July 11 at the age of 86.

Tonegawa was a renowned molecular biologist who wielded his keen insight in a variety of fields, including immunology and neuroscience. In the early 1980s, Tonegawa discovered how the immune system generates its incredible diversity of antibodies — a breakthrough that earned him the Nobel Prize in Physiology or Medicine in 1987.



1994: Tonegawa meets with then Science Dean Bob Birgeneau as they launch the Center for Learning and Memory.

Following that landmark achievement, he turned his attention to neuroscience, where his work has helped to reveal how the brain stores memories as traces called “engrams.”

An MIT faculty member for more than 40 years, Tonegawa also served as the founding director of MIT’s Picower Institute for Learning and Memory and director of the RIKEN Brain Science Institute of Japan, and was a Howard Hughes Medical Institute Investigator.

“Few scientists have reshaped our understanding of biology as profoundly as Susumu Tonegawa,” said Myriam Heiman, director of The Picower Institute. “His intellectual fearlessness, extraordinary creativity, and relentless pursuit of fundamental questions opened entirely new frontiers in both immunology and neuroscience. His influence on science and on the people who had the privilege of working alongside him is immeasurable.”

Drawn to molecular biology

Born in Nagoya, Japan, Tonegawa spent his early years moving between rural towns due to his father’s job as an engineer for a textile company. When it was time for him to go to high school, his parents sent him to a school in Tokyo, where he became interested in chemistry.

He was admitted to the Kyoto University to study chemistry, and while there, he was drawn to the nascent field of molecular biology. He began his graduate studies at the Institute for Virus Research at the Kyoto University, but after only a couple of months, his advisor, Professor Itaru Watanabe, suggested that he apply to a school in the United States, which had more advanced molecular biology programs.

Tonegawa took that advice and was accepted at the University of California at San Diego, where he studied how a virus called phage lambda controls gene transcription. After earning his PhD in 1968, he went on to a postdoc in a lab at the Salk Institute.

In that lab, Tonegawa began studying gene expression of a virus known as SV40. However, his U.S. visa was set to expire at the end of 1970, so he soon headed for a position at the newly established Basel Institute for Immunology in Switzerland.



2005: Tonegawa speaks at a symposium inaugurating MIT’s Building 46. Photo by Justin Knight.

At the time, Tonegawa had little background in immunology, but he soon became fascinated by the 100-year-old question of “antibody diversity” — how the body’s immune system is able to generate hundreds of millions of antibodies from a relatively small set of genes. (The entire human genome contains about 20,000 genes.) That antibody diversity is what allows the immune system to recognize so many pathogens, including those it has never seen before.

(Continued on next page)

With colleagues in Basel, Tonegawa discovered that each antibody protein is not encoded by its own gene — instead, genes for different components of the antibody can be randomly recombined to generate limitless combinations.

In 1987, Tonegawa was the sole recipient of the Nobel Prize for discovering that process, known as V(D)J gene rearrangement. In announcing the award, the Nobel committee noted that Tonegawa's discoveries "explain the genetic background allowing the enormous richness of variation amongst antibodies. Beyond deeper knowledge of the basic structure of the immune system these discoveries will have importance in improving immunological therapy of different kinds, such as for instance the enforcement of vaccinations and inhibition of reactions during transplantation."

From antibodies to engrams

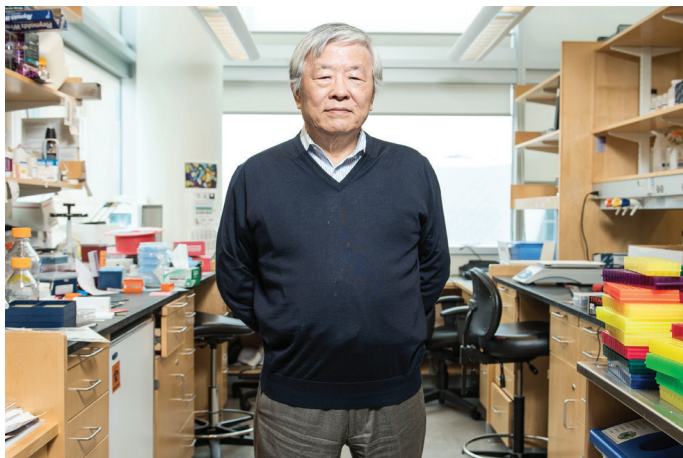
After his groundbreaking antibody discoveries, Tonegawa began to feel the urge to turn to new research directions. He also wanted to return to the United States, so in 1981, he accepted the offer of a professorship at MIT's Center for Cancer Research (today known as the Koch Institute for Integrative Cancer Research). There, he began working on T cells and contributed to scientists' understanding of how T cells are able to generate a large diversity of T-cell receptors.

While at the CCR, he also began to study questions in neuroscience. As he told an interviewer from the Picower Institute in 2022, he was always in search of new scientific endeavors to keep him interested in his work.

"When I decided to become a scientist, my criteria of what to do was whether the scientific problem I got to solve was interesting or not. Whether I'm curious or not. I didn't think about other things like, Could it be too risky? Can I really develop my career by venturing into the field I am not familiar with? That never occurred to me. I just followed my curiosity and instinct," Tonegawa said in an interview published in the summer 2022 Picower Institute newsletter.

In 1994, he was chosen as the founding director for MIT's Center for Learning and Memory, which became The Picower Institute for Learning and Memory in 2002. Tonegawa continued to serve as the center's director until the end of 2006.

Professor Li-Huei Tsai, who succeeded Tonegawa as a Picower Institute director, calls working alongside Tonegawa "one of the greatest honors of my career."



2017: Tonegawa in his lab. Photo by Webb Chappell.



2022: Tonegawa at the Institute's 20th anniversary. Photo by Faith Ninivaggi.

"His passion, boundless energy, and unwavering pursuit of the fundamental mechanisms underlying memory were contagious, inspiring generations of neuroscientists to join and advance the field. Today, we lost a giant. His scientific legacy will continue to shape neuroscience for years to come, and he will be deeply missed by all of us," she said.

Over the past two decades, Tonegawa's lab has made significant discoveries in the field of memory research. In 2013, he and his colleagues reported that they had identified "engrams" in the brain's hippocampus. These engrams consist of episodic memories — memories of experiences — that are stored in specific groups of hippocampal cells. Engrams encode elements including objects, space, and time, linked to a specific experience.

At that time, the researchers also found that it was possible to implant "false memories" in mice by using optogenetics to reactivate an existing engram while the animals formed a new memory. This prompted the mice to associate a new location with the memory of an event that had actually happened in a different location.

Later work from Tonegawa's lab showed that engrams extend beyond the hippocampus and are stored across a widely distributed complex that spans many brain circuits. More recently, he had been working on engrams of "knowledge memory" to decipher the fundamental mechanism of abstract memory. His recent work also delved into how the emotional associations of memories are encoded, and how the brain maintains a timeline of chronological events.

In addition to the Nobel Prize, Tonegawa received many other awards, including the Albert and Mary Lasker Award for Basic Research in 1987, the Bristol-Myers Award for Distinguished Achievement in Cancer Research in 1986, and the David M. Bonner Lifetime Achievement Award from the University of California at San Diego in 2010. He was also known for training many scientists who are now leaders in the field of neuroscience.

Tonegawa was a longtime fan of the Boston Red Sox, and in May 2004, he had the opportunity to throw out the ceremonial first pitch at Fenway Park, as part of the team's tribute to the Boston area's scientific and medical communities.

He is survived by his wife, Mayumi Tonegawa '92, two children, Hidde Tonegawa '09 and Hanna Tonegawa, and two grandchildren. He was predeceased by a son, Satto Tonegawa.

Please watch our website to learn of upcoming commemorative events.

Brain Biomarkers

Brain disorders are notoriously mysterious. To improve diagnosis and to better measure treatment efficacy, Picower Institute labs are developing objective and minimally invasive indicators of brain health.

When you have a sore throat, your doctor can take a swab and culture it to determine if it's strep. When you see something weird on your skin, a dermatologist can take a snip for a biopsy. In both cases, the providers will typically be able to come back to you with an objective, biologically based indication about what's going on with your health and use that to guide your care.

But the brain cannot be swabbed or biopsied. For a long time, psychiatrists and neurologists have had to rely solely on behavioral symptoms, which can be frustratingly subjective and imprecise. In 2010, for instance, Dr. Thomas Insel, then director of the National Institute of Mental Health, called for psychiatry to move from relying solely on symptoms to a basis in genomics and neuroscience to benefit from the same kinds of biomarkers other medical practitioners can employ.

Developing informative, minimally invasive biomarkers of brain health has required years of fundamental research. Scientists have

made headway—for instance by associating certain genetic variations with diseases or disease risk—and indeed a lot of progress is evident in Picower Institute research. Including in some of their most recent studies and current projects, Picower Institute researchers have been developing potential biomarkers for autism spectrum disorders, Alzheimer's disease, bipolar disorder, and even coma and unconsciousness under general anesthesia. Biomarkers not only provide an objective, physical basis for diagnosis, they can also make treatment more personalized and track treatment progress.

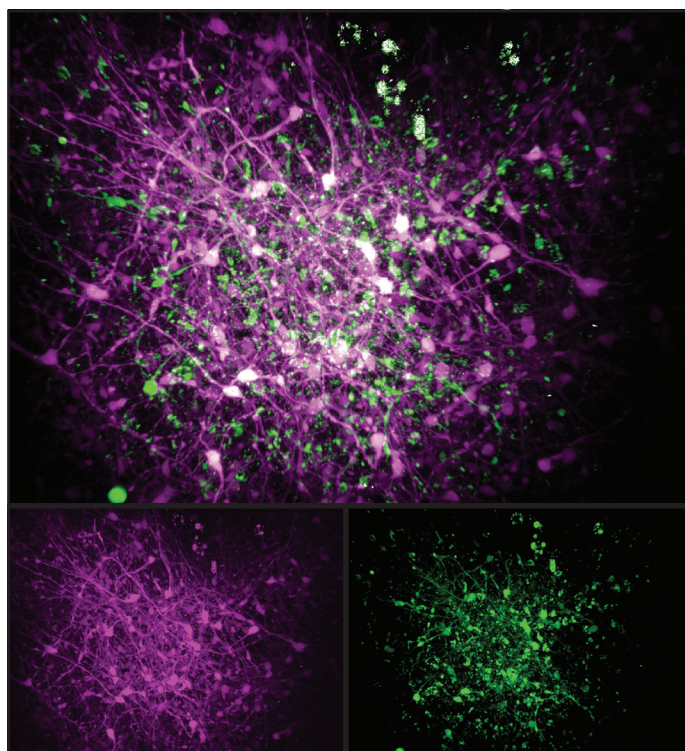
Take the case of bipolar disorder. Because patients exhibit depressive episodes and then sometimes manic ones, they might at first be diagnosed with depression and given related medications which may have side effects, said William R. and Linda R. Young Professor Elly Nedivi. If they first present to a clinician as manic, that could be confused with schizophrenia. And if they see their doctor as a child, either the manic or depressive state might present differently than it would if they were adults. The conflation of age-related changes, potential misdiagnosis, and misdirected medication side effects can all combine to make a correct bipolar diagnosis hard to achieve from snapshots of behavioral observations alone. Except that's pretty much all that's currently available.

"Diagnostics are very complex and really prone to not being correct," Nedivi said. "There is no objective marker."

Genes and risk

To help the 2 percent of the population who experience bipolar disorder, Nedivi's lab has been laying the groundwork to develop genetic biomarkers for bipolar disorder risk. Her lab has shown that specific mutations in a gene called SYNE1 that have been significantly associated with risk for bipolar disorder undermine the expression of a protein called CPG2, potentially affecting communication between neurons. The data her lab has been developing raise the possibility that when a future patient presents to their clinician as either depressed or manic, the doctor will be able to administer a genetic screen that will flag the risk-imparting mutations. This would provide a powerful, objective signal that the real underlying issue might be bipolar disorder, possibly prompting the patient's care providers to consider that diagnosis when they wouldn't have otherwise.

Another disorder where biomarkers are sorely needed is Alzheimer's. While few good treatment options exist, the degenerative nature of the disease means that whatever interventions are tried, they'll be more helpful if they are delivered as early as possible, said Picower Professor Li-Huei Tsai.



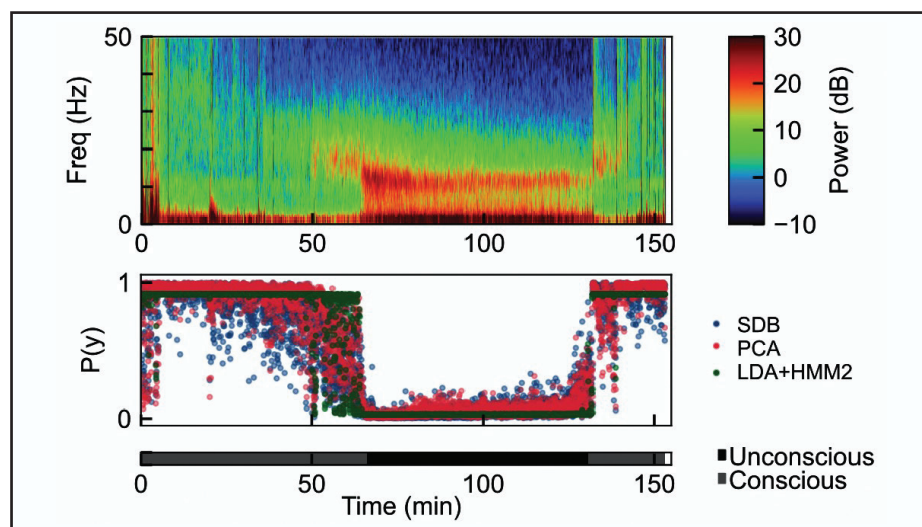
Experiments using "organoid" tissue cultures of Rett syndrome showed that different genetic mutations produce distinct outcomes that benefit from different treatments. Image courtesy of Tatsuya Osaki.

(Continued on next page)

“Biomarkers are accessible and quantifiable,” Tsai said. “Most importantly, they can serve to help early diagnosis—before the appearance of symptoms—for prevention measures.”

Over the last few decades, researchers have identified many Alzheimer’s risk genes. For instance, the largest, the APOE4 variant of the APOE gene, confers a 3-fold risk of developing the disease on people with one allele and a 10-fold risk on those who carry it on both their copies of chromosome 19.

Tsai’s lab has invested heavily in understanding how APOE4 and another genetic risk variant, ABCA7, contribute to Alzheimer’s risk. In several studies over the last several years, her lab has shown that the variants contribute to problematic lipid dysregulation in various cell types in the brain (see our Winter 2025 edition). In a project funded by the Cure Alzheimer’s Fund, Tsai’s lab is investigating whether lipid levels and composition in cerebrospinal fluid (CSF) change with age, sex, APOE variant, and whether someone has Alzheimer’s. Significant changes in CSF lipids could act as accessible biomarkers of disease progression that account for patient sex and APOE variant.



Algorithms developed at The Picower Institute have learned to predict the probability of unconsciousness (bottom row) based on brain waves, as visualized in this spectrogram recorded from a volunteer (top row).

Tsai’s studies of APOE4 and ABCA7 each pointed to a particular nutrient, choline, as a potential treatment to restore normal lipid regulation, at least in some cell types. While one can increase choline by eating eggs, meat, fish, and some beans or nuts, Tsai and colleagues at the University of Texas and MD Anderson Cancer Center have been collaborating to run an early-stage clinical trial testing high-dose choline supplements for six months with APOE4 carriers. One of the first things they are looking for are potential biomarkers accessible through CSF or plasma that would indicate if the nutrient is affecting factors that contribute to Alzheimer’s risk.

Tsai is also developing potential Alzheimer’s biomarkers in two other research collaborations. FINGERPRINT is an AI platform trained on many different Alzheimer’s datasets (e.g. genomic, proteomic, clinical assessments and lifestyle indicators) to produce new integrated, personalized biomarkers that might help predict Alzheimer’s risk. And in a new project funded by the Massachusetts Life Sciences Center, Tsai and MIT Computer Science Professor Manolis Kellis are investigating possible biomarkers that can help women better assess cognitive risks from hormone replacement therapy (see p. 4).

While Alzheimer’s and bipolar disorder are examples of disorders where many genes might contribute to an overall risk, some other conditions have well known single-gene causes. Even then, research is showing, it can be important to go beyond the assumption that dysfunction of the gene is an all-or-nothing problem.

For instance, Rett syndrome is a severe autism-like neurodevelopmental disorder arising from mutations that impede the function of a gene called MECP2. Many lab studies of Rett syndrome, for instance in mouse models or using tissue cultures, simply disable the gene wholesale. But in a study in *Nature Communications* earlier this year, the lab of Newton Professor Mriganka Sur, led by postdoc Tatsuya Osaki, used advanced human “organoid” tissue cultures that blend multiple cell types to investigate the consequences of two different MECP2 mutations. Importantly, they found that each mutation affected the organoids in distinct ways and that rescuing the specific deficits required different interventions. Although there is an overall treatment for Rett syndrome (developed based on Sur’s research), the results suggest that a patient with one Rett-related mutation might also benefit from different treatments than a patient with another one.

Brain Waves

Like Rett syndrome, fragile X syndrome is a neurodevelopmental disorder that arises from mutation and loss of function of a specific gene: FMR1. In fact, it is the most common inherited form of autism. While the gene itself is a biomarker of the disease, it of course does not change during a patient’s lifetime. So what’s needed is a readily measurable biomarker that could help clinicians track the progress of potential therapies, complementing behavioral assessments. Earlier this year in *Nature Communications*, the lab of Picower Professor Mark Bear led by postdoc Sara Kornfeld-Sylla revealed a specific pattern of brain waves, measurable with EEG electrodes on the scalp, that could provide just such a biomarker.

In their study, Bear and Kornfeld-Sylla’s team measured the brain waves of human boys and men, with or without fragile X syndrome, and comparably aged male mice, with or without the genetic alteration that models the disorder. Using a novel analysis approach, Kornfeld-Sylla uncovered specific and robust patterns of differences in low-frequency brain waves between typical and fragile X brains shared between the species at each age range. Moreover, in the mice they showed that the biomarker was able to indicate the effects of even single doses of a candidate treatment for fragile X called arbaclofen.

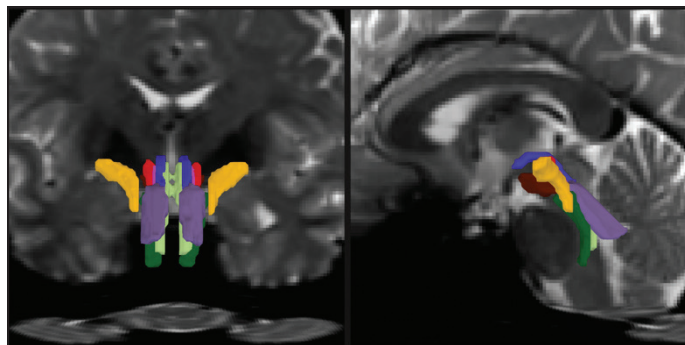
It’s especially exciting that the brain wave biomarker proved to be consistent between mouse models and human patients, Bear said. It raises the possibility that scientists could use it to assess whether potential treatments tried in mice would actually be effective in human patients.

“Because that is something we can measure in mice and humans minimally invasively then you can actually focus the studies to say, OK, drug treatment X affects this biosignature in the mouse. Now let’s go to

(Continued on next page)

the human and see at what dose does that same drug treatment change that same signature,” Bear said. “Then you have a mapping and the mapping can go both ways.”

Brain waves represent the synchronized electrical activity of large groups of neurons that are working together to produce a brain function. That makes them potentially important indicators of a wide variety of brain disorders and states. Sure enough, several other Picower Institute labs are looking to them as biomarkers, too.



Detail from a research figure shows brainstem bundle regions of interest in two different cross-sections of a brain, as automatically determined by the brainstem bundle tool. Image courtesy of Mark Olchanyi.

For instance, more than a decade ago Tsai’s lab noticed that the power and synchrony of a specific “gamma” frequency brain wave (40Hz), was reduced in Alzheimer’s model mice and in human patients. Curious to see if interventions that increased the wave’s power and synchrony could affect disease, Tsai’s lab experimented with exposing mice to 40Hz sensory stimulation (first light, then sound, and later tactile vibration). Numerous studies since 2016 by Tsai’s lab and others have shown important disease-fighting effects in mice (and in preliminary studies in humans). An MIT spinoff Cognito Therapeutics is wrapping up a pivotal nationwide trial with human volunteers this fall.

The research has revealed that reduced 40Hz power and synchrony may be a biomarker for Alzheimer’s, though Tsai cautions that it would need to be combined with other biomarkers and traditional cognitive assessments to produce a reliable diagnosis. But as a potential treatment, it also creates a need for biomarkers to measure its efficacy. In ongoing human trials at MIT, Tsai’s lab is monitoring a range of potential measures including MRI, EEG, and blood tests to see which physical needles 40Hz sensory stimulation moves. In a very small recent study in *Alzheimer’s & Dementia: The Journal of the Alzheimer’s Association*, the lab reported that two patients who used 40Hz sensory stimulation for two years showed reductions on a new industrywide biomarker, blood-based measures of the protein pTau-217.

For years, Institute Professor Emery N. Brown, an anesthesiologist, neuroscientist and statistician, has advocated that brain waves can act as personalized biomarkers of unconsciousness under anesthesia. Traditionally anesthesiologists have used body-based indicators of unconsciousness (e.g. lack of movement, heart-rate variability) but Brown points out that general anesthetics act most directly on the brain. He has published numerous studies showing that EEG measurements of brain waves can be used to reliably read out a patient’s degree of unconsciousness. He’s demonstrated, for instance with colleagues last year in a study in *JAMA Pediatrics*, that EEG can guide anesthesiologists to safely reduce drug dose during surgery to prevent needless overdosing in children that leads to post-operative side effects, such as delirium.

Over the last several years, Brown has joined forces with Picower Professor Earl K. Miller in these studies. Last year in *Cell Reports*, their labs showed that even among different anesthetic drugs, with their varying molecular mechanisms of action, they all have the same effect at the level of brain waves—they throw them out of phase with each other within the same brain hemisphere, thereby disrupting communication across the brain’s surface, or cortex. That turns out to be an apparently universal signature of unconsciousness (Miller has also shown this by a different measure working with MIT colleague Ila Fiete).

Brain waves are such a clear and powerful biomarker of unconsciousness under anesthesia that Brown and Miller have been able to devise a closed-loop system that can read out brainwaves and then automatically adjust dosing to maintain a target level of consciousness. They hope to someday deploy such systems in operating rooms to assist anesthesiologists.

Brain Imaging

Brown’s lab also broke new ground last year by showing that imaging of the brainstem could deliver biomarkers for a variety of neurological conditions. The brainstem’s many bundles of nerve fibers help to govern essential functions such as consciousness, sleep, breathing, heart rate and motion. Because those bundles are small and tightly packed together, they’ve been very hard to image. But in a study in the *Proceedings of the National Academy of Sciences*, then graduate student Mark Olchanyi showed how he used AI to distinctly resolve eight brainstem bundles from live diffusion MRI images. Moreover, he demonstrated that retrospective analyses of images from patients using his “Brainstem Bundle Tool” could identify potential biomarkers of Parkinson’s disease, multiple sclerosis and traumatic brain injury. He even showed how the system could track the internal healing of a coma patient. The improvements visible in the imaging tool correlated with the improvement that enabled the patient to wake up after 7 months.

In another imaging advance, Sur and Osaki published a study last year in *Light: Science & Applications* that could yield another potential biomarker. With MIT Mechanical Engineering colleagues, the team invented a new microscope system that can peer especially deep into living brain tissue. The “photoacoustic” scope, which sends in light but measures sound coming out, was able to detect NAD(P)H, a molecule tightly associated with cell metabolism in general and electrical activity in neurons in particular. 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 microscope needs more development before it could be used to image live human brains (for instance during surgeries), but like the other innovations above, it shows that, with research, scientists are finding many ways to help clinicians go beyond subjective symptoms. Biomarkers will increasingly make a mark on neurological and psychiatric care.

Upcoming **EVENTS**

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



THE AGING BRAIN INITIATIVE FALL 2026 SYMPOSIUM

Innovation for the Aging Brain

Friday, September 25, 2026 | 1:00 - 6:00pm | MIT Building 46, Singleton Auditorium (46-3002)

Alan Jasanoff
McGovern Institute,
MIT Biological Engineering

Oleta Johnson
MIT Chemistry

Laura Kiessling
MIT Chemistry

Earl K. Miller
MIT Picower Institute
for Learning and Memory

Ritu Raman
MIT Mechanical Engineering

Giovanni Traverso
MIT Mechanical Engineering



REGISTRATION REQUIRED



THE 2026 PICOWER LECTURE WITH RICHARD HUGANIR

JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

WEDNESDAY, OCTOBER 28 AT 4:00PM
SINGLETON AUDITORIUM (46-3002)



Massachusetts
Institute of
Technology



THE PICOWER
INSTITUTE
FOR LEARNING AND MEMORY



Nov. 4, 2026

The Picower Institute Fall
2026 Symposium

Comparative
Neuroscience: Lessons
from Biodiversity

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

picower.mit.edu



Neuroscience News Fall 2026



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.

SUPPORT THE PICOWER INSTITUTE

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.

HOW TO SUBSCRIBE

Subscriptions to Neuroscience News are available at no charge in print or PDF form. To subscribe, send your mailing or email address to: Darnell Reese, drreese@mit.edu, Tel: 617-452-2485.

EDITORIAL CONTRIBUTORS

David Orenstein and Anne Trafton

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; **Emery Brown**, Institute Professor; Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience, Department of Brain and Cognitive Sciences, Institute for Medical Engineering and Science; **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 for Medical Engineering and Science; **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**, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Director, The Picower Institute for Learning and Memory; **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**, Pfizer-Laubach 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** (in memoriam), 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; **Brady Weissbourd**, Thomas D. and Virginia W. Cabot Assistant Professor of Biology; **Matthew Wilson**, Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology