A new director

Myriam Heiman becomes the fourth director of The Picower Institute, succeeding Li-Huei Tsai. She shares her outlook in a Q&A on page 9.

Neuroscience News

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THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY

DIRECTOR'S **MESSAGE**

Dear Friends,

I'm very pleased to meet you and deeply honored to take on the role of The Picower Institute director, succeeding Li-Huei Tsai, and Mark Bear and Susumu Tonegawa before her. "Succeed" is indeed the perfect word because together, their leadership built The Picower Institute into a marvelously successful neuroscience research institution. The Picower Institute has an extraordinary legacy. With humility and enormous enthusiasm, I'm eager to do everything I can to help support the next generation of transformative research.

I still remember arriving at The Picower Institute in 2011 as a new faculty member, after my graduate studies at Johns Hopkins and postdoctoral work at Rockefeller University. I came to MIT because of its highly collaborative environment, with exceptional cross-disciplinary strengths across engineering, neuroscience, biology, and biomedical research.

Indeed, this place has proved to be incredibly special. Picower Institute labs have produced enormously influential insights into memory, consciousness and anesthesia, cognition, perception, behavior, and development, while also advancing knowledge and therapeutic strategies for autism, amblyopia, bipolar disorder, Rett syndrome, Down syndrome, mood disorders and neurodegenerative diseases from Huntington's disease to Alzheimer's disease. Picower scientists are also remarkable innovators, frequently developing new tools and technologies that expand what is possible in neuroscience research. In this edition of our newsletter alone, you will find stories that reflect the breadth, depth, and impact of the work our faculty, students, and staff pursue every day.

It's very important to me, and to all of us, to recognize that we don't do this work alone. You are our partners in discovery. Your interest in and support for our research are essential, now more than ever, and we are deeply grateful for your commitment to our mission. As I take on the responsibility to support the Institute's exceptional scientists and trainees in their quest for discoveries that deepen our understanding of the brain and improve human health, I could not be more excited or more grateful.

MYRIAM HEIMAN, DIRECTOR

The Picower Institute for Learning and Memory

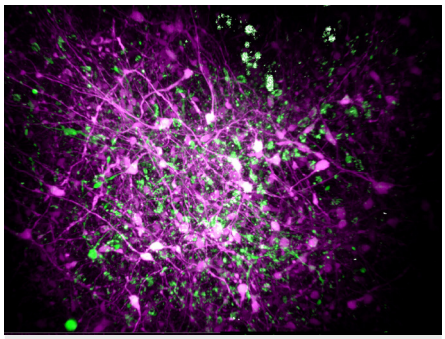
Rett study highlights potential for personalized treatment

Rett syndrome arises from mutations in the MECP2 gene. A new study by Picower Institute neuroscientists shows that two different mutations caused many distinct abnormalities in lab cultures and that correcting key differences made by each mutation required different treatments.

"Individual mutations matter," said Mriganka Sur, senior author of the new study in *Nature Communications* and Newton Professor in The Picower Institute. "This is an approach to personalizing treatment, even for a single-gene disorder."

The study employed advanced 3D human brain tissue cultures called "organoids." Lead author Tatsuya Osaki, a Picower Institute research scientist, said that the organoids enabled him to gain mutation-specific insights that haven't emerged in prior studies where scientists have just knocked out MECP2 overall. The organoids also provided a novel opportunity to understand how each mutation affected different cell types and their interactions.

More than 800 mutations in MECP2 can cause Rett syndrome, but just eight account for more than 60 percent of cases. Sur and Osaki chose one of these, R306C, which involves a difference of just one DNA base pair, because it represents 7-8 percent of Rett syndrome cases. The other mutation they chose, V247X, is much more rare and severe.



Purple staining highlights excitatory neurons, while white staining labels inhibitory neurons in a Rett syndrome organoid. *Credit Tatsuya Osaki.*

In organoids cultured for three months, each mutation produced some common but also sometimes distinct changes in organoid structure, activity and connectivity compared to control organoids with non-mutated MECP2. Ultimately the team found that an HDAC2 inhibitor drug helped R306C organoids and the GABA "agonist" drug baclofen helped the V247X organoids.

Leaky brain blood vessels in Rett syndrome

MIT researchers have discovered that two common genetic mutations that cause Rett syndrome each set off a molecular chain of events that compromises the structural integrity of developing brain blood vessels, making them leaky. The study traces the problem to overexpression of a particular microRNA (miRNA-126-3p), and shows that tamping down the miRNA's levels helps to rescue the vascular defect.

Rett syndrome is a severe developmental disorder affecting both the brain and body. It is caused by various mutations in the widely expressed MECP2 gene, but the first symptoms don't become apparent until affected children (mostly girls) reach 2-3 years of age. Because that's a critical time in development for the brain's blood vessels, neuroscientists in The Picower Institute for Learning and Memory embarked on a study to model how two common but distinct MECP2 mutations may affect vascular development and contribute to the disease's profound neurological pathology.

To conduct the research published in *Molecular Psychiatry*, lead author Tatsuya Osaki and senior author Mriganka Sur developed advanced human tissue cultures to model vessel development, with and without the MECP2 mutations. The cultures not only enabled them to model and closely observe how the mutations affected the vessels, but also allowed them to molecularly dissect the problems they observed and then to test an intervention that helped.

"A role for microRNAs in Rett syndrome has been shown, but now demonstrating that miRNA-126-3p is actually downstream of MECP2 and directly implicated in the endothelial cell dysfunction is an important piece of the Rett syndrome puzzle," said Sur, Newton Professor of Neuroscience in The Picower Institute.

Different **anesthesia** drugs affect the brain the same way

When patients undergo general anesthesia, doctors can choose among several drugs. Although each of these drugs acts on neurons in different ways molecularly, they all lead to the same result: a disruption of the brain's balance between stability and excitability, according to a new MIT study.

This disruption causes neural activity to become increasingly unstable until the brain loses consciousness, the researchers found. The discovery of this common mechanism could make it easier to develop new technologies for monitoring patients while they are undergoing anesthesia.

"What's exciting about that is the possibility of a universal anesthesia-delivery system that can measure this one signal and tell how unconscious you are, regardless of which drugs they're using in the operating room," says Earl Miller, Picower Professor in The Picower Institute for Learning and Memory.

Miller, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience Emery Brown, and their colleagues are now working on an automated control system for delivery of anesthesia drugs, which would measure the brain's stability using EEG and then automatically adjust the drug dose.

Miller and Ila Fiete, a professor of brain and cognitive sciences, are the senior authors of the study in *Cell Reports.* Former graduate student Adam Eisen is the paper's lead author.

Exactly how anesthesia drugs cause the brain to lose consciousness has been a longstanding question in neuroscience. In 2024, a study from Miller's and Fiete's labs suggested that for propofol, the answer is that anesthesia works by disrupting the balance between stability and excitability in the brain. The researchers found that propofol knocks the brain out of this state, known as "dynamic stability." As doses of the drug increased, the brain took longer and longer to return to its baseline state after responding to new input. This effect became increasingly pronounced until consciousness was lost.

In their new study, the researchers used the same technique to measure how the brain responds to not only propofol but two additional anesthesia drugs — ketamine and dexmedetomidine. This study showed that the same destabilization induced by propofol also appears during administration of the other two drugs.

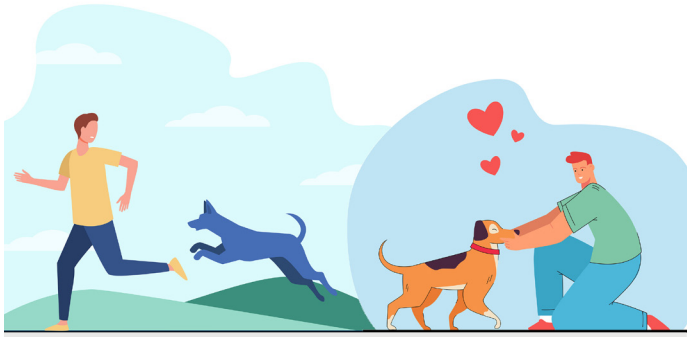
How our brains use **categories** to make sense of the world

In the new review article, "Categorization is Baked into the Brain," cognitive scientists Lisa Feldman Barrett, University Distinguished Professor at Northeastern, and Earl K. Miller, Picower Professor at MIT, contend that categorization is part of a predictive process the brain uses to efficiently meet the body's needs in a fast-paced, otherwise overwhelming sensory world. In that sense, their paper in *Nature Reviews Neuroscience* challenges decades of dogma about how and why the brain boils down what it sees, hears, smells, tastes and feels.

Categories are groups of things that are similar enough to be considered functionally equivalent. When you walk through a neighborhood, you'll naturally experience the furry, four-legged, barking animal ahead of you as a "dog." In the classic view of cognition, your brain arrives at that categorization by soaking in lots of basic sensory features of the hound—its shape, its size, the sounds it makes, its behavior—and compares that to some prototype "dog" stored in your memory. Hundreds of milliseconds after the first sensory inputs, you can then decide what you might want to do about the dog.

Barrett and Miller argue that's wrong. Instead, they propose that your brain comes prepared for sensory patterns with predictions of the motor action plans that are most likely to achieve the needs and goals you bring to the moment. Those prediction signals can be described as a momentary category that the brain constructs to shape the processing of sensory signals. From the very start, incoming sensory signals are compressed and abstracted into that category to efficiently select the best predicted plan. If you are in an unfamiliar neighborhood your brain might construct the category "dog" to avoid being bit, resulting in: "back away slowly while saying nice doggie." If you are on your own block and encounter a familiar dog, your brain might construct a category to kneel and open up your arms to summon your neighbor's adorable pup for a satisfying petting.

In either case, the category "dog" arises in the context of your needs and your prediction from a menu of learned action plans for similar situations, not from some intellectual exercise of neutrally regarding sensory inputs, comparing them to a fixed prototype, and then planning from there. If the brain really worked the classically believed way, you'd be on the back foot when the unfamiliar dog lunged at you.



The category "dog" may be constructed based on the action plan you come prepared with, given the circumstances you are in and the predictions you make.

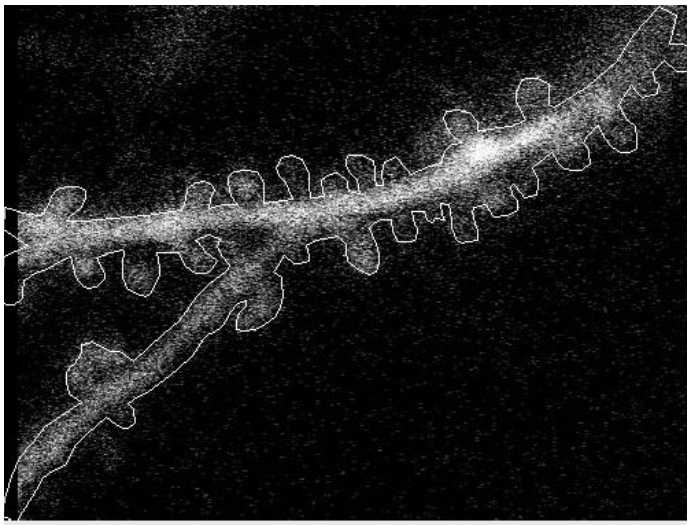
The rules neurons follow to make sense of what we see

Even in the visual cortex, a brain region named for its specialized role in processing basic features of what the eyes see, not every neuron ends up answering the call to process properties of visual input. Maybe that's because each neuron receives a wide variety of inputs via thousands of circuit connections, or "synapses," and has to opt to respond to the visual information vs. something else. In a new study in mice, neuroscientists at The Picower Institute reveal how neurons that perform visual processing bring order to this input to get the job done.

Neuroscientists are keenly interested in what inputs, from among so many choices, will compel neurons to participate in the brain's computations and functions, said senior author Mriganka Sur, Newton Professor in The Picower Institute. Neurons ultimately participate in brain circuits by "firing" an electrical action potential.

"The configuration of inputs, the kind of organization, the assembly of neurons that modulate each other to generate an action potential is the essence of how brain circuits process information," Sur said. "These (visual cortex) cells are a microcosm of this very profound and big picture of neuroscience."

In the study in *iScience*, led by postdoc Kyle Jenks, the research team achieved their findings by meticulously imaging how the neurons' cell bodies (or somas) and their individual synapses (formed on protrusions known as dendritic spines) responded as mice viewed moving images. They did this imaging not only for visually responsive neurons, but also for unresponsive neurons that nevertheless have visually responsive spines. That allowed them to analyze many key properties that might influence where a particular synapse forms, and how it influences responses at the cell body.



White indicates an electrical signal extending back from the cell body through a dendrite, reaching synapses on the dendrite's spines. *Credit Kyle Jenks*

"Our results reveal that synaptic inputs to excitatory layer 2/3 neurons in mouse (visual cortex) are not randomly arranged, but organized and distributed in a manner that correlates with multiple factors including somatic responsiveness, somatic tuning, branch type, distance from the soma, local correlations, and stimulus selectivity," the researchers wrote.

First AI foundation model for Alzheimer's prevention

Alzheimer's disease is best addressed as early as possible, ideally before symptoms become apparent. To enable early, accurate risk prediction both for individuals and whole populations, a team of AI researchers, physicians, and scientists centered at MIT has released FINGERS-7B, the first AI foundation model built to make Alzheimer's preventable. The team presented the model at ICLR, one of the largest AI conferences, April 27 in Rio de Janeiro

FINGERS-7B integrates lifestyle, clinical, genomic, and proteomic data from tens of thousands of at-risk individuals to discover "multi-omic" biomarkers for preclinical Alzheimer's. On WW-FINGERS network datasets, it delivers 4× more accurate preclinical diagnosis and 130% better responder stratification than prior art.

The model is open source and is deployed in the AD Workbench, the secure cloud environment operated by the Alzheimer's Disease Data Initiative (ADDI) and used by Alzheimer's researchers worldwide.

FINGERPRINT pairs FINGERS-7B with AI agents that run automated multi-omic analyses. The model was trained on data from tens of thousands of people at risk for Alzheimer's, and learns jointly from lifestyle, clinical, biomarker, genomic, and proteomic signals. The novel concept is the multi-omic biomarker. Instead of reading one omics domain at a time, FINGERS-7B reads them together. That is what makes earlier and more accurate detection possible.

"Each of us carries a biological fingerprint, basically a unique combination of signals that reveal disease risk and, if properly understood, could enable prevention and treatment of Alzheimer's disease," said Adrian Noriega, MIT-Novo Nordisk AI Fellow and FINGERPRINT co-lead with Arvid Gollwitzer, Broad Institute research scholar, who led the design and training of FINGERS-7B.

MIT's Aging Brain Initiative, directed by Picower Professor Li-Huei Tsai, seeded the effort last June with a $100,000 grant to Noriega and Giovanni Traverso, Professor of Mechanical Engineering.

"Even as Alzheimer's research labs like ours have gained the capability to generate huge volumes of data, including genetic, epigenetic and proteomic profiles from human tissue samples, we've faced the challenge of truly integrating all of it to gain a comprehensive view of individuals' risk, prognosis and likely treatment response," Tsai said.

Neurons sense bacteria in the gut

The human gut microbiome has been associated with both depression and Parkinson's disease. To understand the actual mechanisms that enable the bacteria to influence brain function, a new study by Picower Institute neuroscientists examines how neurons sense bacteria in a model organism, the nematode *C. elegans*.

Led by postdoctoral Picower Fellow Cassi Estrem in the lab of Associate Professor Steven Flavell, the study in *Current Biology* identifies the specific chemicals that a key neuron in *C. elegans* senses both in the bacteria that it eats as well as in the bacteria that it needs to avoid ingesting.

"In our bodies, our own cells are outnumbered by the bacterial cells living in and on us. There's an increasing recognition that this has a profound impact on human health," said Flavell.

Achieving a fundamental mechanistic understanding of how neurons interact with bacteria could help improve attempts to intervene in or manipulate those interactions with therapeutic drugs or supplements, Flavell said.

In the study the team broke bacteria down into specific chemical components to see which one or ones triggered the neuron. They found that polysaccharide sugars drove neural activation in bacteria the worm eats. Meanwhile in a bacterium the worm avoids, the trigger was a chemical called prodigiosin.

Flavell says it's likely that some of the fundamental mechanisms highlighted in the paper will inform studies of similar mechanisms in other animals: "We developed a way of identifying these pathways by studying this organism that specializes in bacterial detection and displays robust responses. But there's no reason these pathways should be limited to *C. elegans*. The molecular players we identified are found in many species, including mammals."

Turning **worms**: from brains to behaviors

Animal behavior reflects a complex interplay between the animal's brain and its sensory surroundings. Only rarely have scientists been able to discern how actions emerge from this interaction. A new study in *Nature Neuroscience* by Picower Institute researchers offers one example by revealing how circuits of neurons within *C. elegans* worms respond to odors and generate movement as they pursue smells they like and evade ones they don't.

"Across the animal kingdom, there are just so many remarkable behaviors," said study senior author Associate Professor Steven Flavell. "With modern neuroscience tools, we are finally gaining the ability to map their mechanistic underpinnings."

By the end of the study, which former graduate student Talya Kramer led as her doctoral thesis research, the team was able to show exactly which neurons in the worm's brain did which of the jobs needed to sense where smells were coming from, plan turns toward or away from them, shift to reverse (like old-fashioned radio-controlled cars, *C. elegans* worms turn in reverse), execute the turns, and then go back to moving forward. Not only did the study reveal the sequence and each neuron's role in it, but it also demonstrated that worms are more skillful and intentional in these actions than perhaps they've received credit for. And finally, the study demonstrated that it's all coordinated by the neuromodulatory chemical tyramine.

A *C. elegans* worm caught in mid-turn. *Credit Talya Kramer*

"One thing that really excited us about this study is that we were able to see what a sensorimotor arc looks like at the scale of a whole nervous system: all the bits and pieces, from responses to the sensory cue until the behavioral response is implemented," Flavell said.

As worms and jellyfish **wriggle**, AI tools track neurons

Understanding the connection between behavior and brain cell activity is a major goal of neuroscience. In a new study in *eLife*, MIT neuroscientists debut three AI-infused tools to accurately track neural location, identity and activity even as animals wiggle and warp during their complex movements and behaviors.

"In a live behaving animal, we can now keep track of neurons over time and even determine the exact identities of most neurons," said study senior author Associate Professor Steven Flavell.

The three tools are "BrainAlignNet," which can keep track of cells throughout a long time series of images, such as a video; "AutoCellLabeler," which can identify the cell types in each image, if cued with some initial training; and CellDiscoveryNet, which can identify the cell types without any training or supervision.

The capability of the tools, which have largely ended the lab's need to choose between speed and accuracy, Flavell said, provides a potential model for how other labs working with other large series of images—in human tissues or samples from other organisms—can approach the problem of identifying cell types and keeping track of them across many images.

Indeed, while Flavell's lab focuses on the roundworm *C. elegans*, the study applied BrainAlignNet to jellyfish in the lab of Picower Institute colleague and study co-author Brady Weissbourd. Former graduate student Adam Atanas led the work.

Symposium: How understanding the brain could improve the functioning of **democracy**

The May 19 symposium "The Neuroscience of Democracy" brought neuroscientists, social scientists and civic leaders together to build conceptual bridges between brain research and public affairs.

"We don't typically consider how the brain is not only the basis of ourselves, but also the basis of our societies," acknowledged Li-Huei Tsai, Picower Professor of Neuroscience, in her opening remarks. "Our institutions are our creations and our participation in them is our choice. They emerge from, and are sustained by, our needs, our cognition, our beliefs, and our behavior."

Felicia Wong and Stacey Abrams in conversation. *Photos by Faith Ninivaggi*

More than 300 people registered to attend the event, organized in collaboration with The Freedom Together Foundation (FTF), a charitable foundation that works to create a more democratic, inclusive, and sustainable society and supports The Picower Institute. The Picower Institute was established in 2002 with a gift from Jeffry and Barbara Picower.

Several speakers who've spent their careers working on civic issues in communities around the United States emphasized that democratic participation stems at least as much from emotion as from a rational calculation of self-interest.

When FTF President Deepak Bhargava was teaching at the City University of New York, his research asked how democratic movements could engender as strong an emotional attachment as authoritarian movements seem to do. Central to this work, he said, is a need to critique a "rationalist fallacy" that pervades public affairs analysis. Bhargava said that after years as a community organizer where he's seen the importance of emotion and a sense of group belonging, he's routinely surprised by the shock of others when citizens vote against their own financial interests.

"This way of viewing people and their motivations is an obstacle to understanding and engagement with them and it's predicated on an economistic model of understanding human motivation that is just wrong," he said.

In an on-stage dialogue with FTF Senior Fellow Felicia Wong, voting rights advocate and author Stacey Abrams recounted the multifaceted role of emotion throughout her 2018 gubernatorial campaign in Georgia. Her inspiration to run was the rage she felt when as minority leader in the state's House of Representatives she couldn't prevent a set of tax policy changes that she found regressive. But Abrams also said motivating voters derived from appealing to a more positive emotion: a feeling of possibility. More than trying to change anyone's political beliefs, she said, the campaign sought to broaden voters' perspectives.

"By my very presence I was proof of a different way to think about the world," she said. "I connected that to their lived experience and I met them where they were."

Alicia Garza, FTF Senior Vice President for Movement Infrastructure and Explorations, described the central importance of hope in civic engagement. Referencing life-and-death anecdotes from the Civil Rights Movement of the 1950s and 1960s, to the Black Lives Matter movement she co-founded, to civic action in Minnesota last year, Garza said the common thread that maintained people's courage was hope.

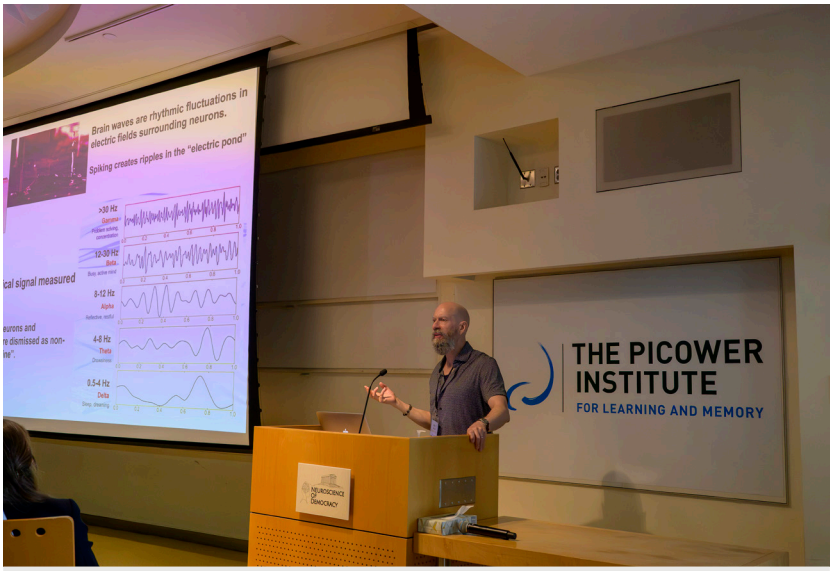
"One of the things we know from studies of social change long-term is that oftentimes, yes, people come into protests or movements because they're angry about something, but that does not sustain them," Garza said. "What sustains them is hope."

In her work as a Harvard political science professor and democracy advocate, Danielle Allen, too, said she's seen the importance of emotion in the electorate. Allen described her research showing that half the states (blue and red ones alike) in the country doubly disenfranchise voters via closed primaries with limited competition among candidates (In his talk, Princeton neuroscience professor Sam Wang pointed out structural problems in elections—particularly gerrymandering—mean that in 90 percent of Congressional districts a primary is perhaps the only competitive election).

Part of restoring the function of democracy, Allen said, is reconnecting voters to a sense of agency, encouraging them to "multitask" so that they take on civic engagement as well as the normal activities of their daily lives, and to enhance their ability to build bridges and coalitions with unfamiliar people. She called for neuroscience research that could provide fundamental understanding of such emotions and cognition.

Several of the symposium's neuroscientist speakers shared ways in which their research is beginning to speak to such issues.

Tali Sharot of University College London and MIT's Brain and Cognitive Sciences (BCS) Department presented research showing that people sometimes prioritize feelings of affinity over objective information and their own rational self-interest. For instance, she showed that people performing a task (and being rewarded for accuracy), would ask for help from people shown to have the same political leanings over people who were actually performing the task better. To try to dispel such confirmation biases in the online sphere, Sharot's lab is experimenting with technology that objectively labels websites via a browser plugin to rate their information quality, sentiment and instrumental utility.



Earl Miller discusses how the brain produces thought, and does so more efficiently than AI

In her talk, BCS Professor Rebecca Saxe emphasized that democracy doesn't require people to agree on everything. More than a decade ago labs began studying brain activity patterns underlying empathy but Saxe said she now realizes that what would better serve studies of democracy are not cases in which people share the same feelings ("empathy"), but instead where people attempt to understand what others think ("respect"). She presented data from fMRI studies showing that brain regions involved in considering the thinking of others are independent from regions involved in empathy.

Emily Falk of the University of Pennsylvania noted that a crucial behavioral tool people have to bridge differences is conversation. Her research on improving conversation for civic engagement dovetailed with several themes of the day. For instance, she cited research showing how differing political backgrounds shape neural responses to the same media and discussed several specific neural correlates of activity associated with willingness to engage in discussions of policy issues. Her lab has found that strangers and friends alike enjoy conversation more when they explore new ground together. And in negotiations, they will do that more when they are instructed to compromise than to persuade.

Given the sheer scale of the electorate, many democracy researchers are considering how and whether artificial intelligence can help facilitate dialogue and overcome misinformation.

MIT political science Professor Lily Tsai, described her lab's work harnessing AI to facilitate engaging virtual spaces for political dialogue. Importantly, as in a physical town meeting, participants retain the agency and freedom to become as involved as they want to be—engaging directly in debate vs. merely observing generated overviews and summaries. Accounting for how people want to engage, and using AI to facilitate that, can potentially improve the quality of debate over what plays out in current social media. But, as Allen did, she called on neuroscientists to help.

"Neuroscience has a lot to tell us about the kinds of signals and stimuli that make people more likely to experience a sense of safety rather than threat in an environment with unfamiliar people or people with opposing views," she said. "It might also help us understand the kinds of stimuli and environments that make people more likely to experience a feeling of autonomy and control, and what makes people more likely to view difference with curiosity and respect."

In his talk, MIT political science colleague Adam Berinsky discussed his research into combatting misinformation that erodes trust in important institutions. It's not necessarily easy to dissuade someone who has become dug in to a belief in a conspiracy theory, he said, but he's finding that AI-powered tools can successfully engage people in productive one-on-one dialogues. Even so, he cautioned, trust in AIs can shift.

However AI is used, said Picower Professor Earl K. Miller, it would be far less disruptive to the environment and to communities grappling with the presence of massive data centers if it actually worked more like the brain does. Miller described how the brain manages on a mere 20 Watts of power to achieve greater intelligence than AI. The brain controls its billions of connected neurons to produce consciousness and cognition with traveling waves of electrical activity, he said. The brain therefore engages in very efficient analog computation, whereas AIs rely on energy-intensive digital computation. He called for sustained funding of basic science research, noting that it has not only helped him explain how biological intelligence works but also highlight how AI could work better.

In concluding remarks, Picower Institute director Myriam Heiman noted that democracy and scientific discovery historically have thrived together in cultures that value openness to new ideas and evidence, and tolerance for dissent. She said she drew hope from how the symposium highlighted ways in which efforts to strengthen democracy can draw on science.

"Understanding how people think, connect, fear, trust, learn and cooperate may help us design institutions and cultures that better align with the realities of human behavior rather than some idealized assumption about it," said Heiman, John and Dorothy Wilson Professor.

After 16+ years leading Picower Institute, Tsai will sharpen focus on research, teaching

Picower Professor Li-Huei Tsai, who has led The Picower Institute since 2009, stepped down from the role of director at the end of June. Her decision frees her to focus exclusively on her academic work, including her continued leadership of MIT's Aging Brain Initiative and the Alana Down Syndrome Center.

"During her exceptional 16-year tenure in the role of director, Li-Huei has led substantial growth at The Picower Institute," says Nergis Mavalvala, Dean of the School of Science. "She has markedly expanded the faculty—eight of the current 16 labs joined Picower under her directorship—through successful recruitment of highly talented neuroscientists. She has done this, and more, all while leading one of our most productive and influential labs, working on a quintessentially grand challenge in human health: combatting Alzheimer's disease."

Picower Professor Li-Huei Tsai

Tsai says she is grateful to have had the opportunity to build The Picower Institute into a preeminent center for neuroscience research.

"I'm immensely proud of what our Institute represents: world-renowned neuroscience research that is creative, rigorous, novel and impactful," Tsai says. "Our labs produce innovations, discoveries and often translational strategies that have broken new ground and pushed science, medicine and technology forward. We also provide excellent training that has enabled us to launch the careers of many of the field's new and future leaders. It has been a tremendous honor to be able to build on the incredible foundation and inspiration provided by my predecessors Susumu Tonegawa and Mark Bear to enable the institute's growth and success."

Founded by Tonegawa as the Center for Learning and Memory in 1994 and then renamed The Picower Institute for Learning and Memory after a transformative gift by Barbara and Jeffry Picower in 2002, the institute now comprises about 400 scientists, students and staff across 16 labs in MIT's Buildings 46 and 68.

But when Tsai became director in July 2009, The Picower Institute comprised 11 labs and a community closer to 200 members. Tsai worked closely with the Picowers' foundation, formerly the JPB Foundation and now the Freedom Together Foundation, to develop several strategic initiatives to accelerate growth and enhance research productivity. These have included programs specifically designed to support junior faculty, to catalyze more applications for more private grant funding, and to sustain fellowships for more than 18 postdocs and graduate students. Working with the foundation, she has also expanded the scope of research support provided by the Picower Institute Innovation Fund begun under Bear.

To galvanize MIT colleagues to fight neurodegenerative diseases and neurological disorders affecting cognition, Tsai also built two campuswide initiatives: The Aging Brain Initiative, founded in 2015 and sustained by a broad coalition of donors, and the Alana Down Syndrome Center, established in 2019 with a gift from The Alana Foundation.

Tsai's research has grown, too. She has led numerous highly cited discoveries about the neurobiology of Alzheimer's disease and has translated several of these insights into specific therapeutic strategies, including one now in a pivotal clinical trial (audiovisual stimulation of the brain's 40Hz gamma frequency rhythm). She has published more than 230 peer-reviewed neuroscience studies, generated numerous patents and launched several startups. Among many honors, she has been named a fellow of the National Academy of Medicine, The American Academy of Arts and Sciences, and the National Academy of Inventors.

"After 16 years leading The Picower Institute, I'm now eager to sharpen my focus on advancing human health through the work in my lab, the Aging Brain Initiative and the Alana Center," Tsai said.

Congratulations, Picower People!

- **Emery N. Brown,** Edward Hood Taplin Professor, earned an honorary doctorate from Yale May 18. Yale President Maurie McInnis said as Brown received the degree: "Your groundbreaking research has revolutionized how we understand the brain at its most mysterious edges, through rigorous statistical modelling and elegant experimentation. You have revealed anesthesia, not as a blunt shutdown of the mind, but a structured, dynamic reorganization of brain activity. Your work has uncovered new ways to study a range of effects in the brain including mental illness."
- Assistant Professor **Brady Weissbourd** has been awarded the Thomas D. and Virginia W. Cabot Professorship in recognition of his excellence in teaching and research.
- Picower postdoctoral Fellow **Takato Honda** and Picower Institute HR Business Partner **Savanna Fusco** each received Infinite Expansion awards from the MIT School of Science May 21. Honda's mentor, Sherman Fairchild Professor Matt Wilson said, "Takato is a talented scientist, a rigorous and creative thinker with exceptional curiosity and a passion for science, a dedicated teacher and mentor." Former Picower Institute Director Li-Huei Tsai praised Fusco's "ability to build relationships grounded in trust, responsiveness, and practical problem-solving."
- Graduate students in Picower labs recently earned their doctoral degrees including **Drs. Taylor Baum, Daniel Cho, Adam Eisen, Jordan Harrod, Mark Olchanyi and Albert Wang.** Congratulations all!

3 Questions with Myriam Heiman: The Picower Institute's New Director

Professor Myriam Heiman shares her outlook on the promise of basic and translational neuroscience, the Institute's great potential to help deliver on it, and what's needed now to make that happen.

On July 1, Professor Myriam Heiman took the reins of The Picower Institute for Learning and Memory from Picower Professor Li-Huei Tsai, who served in the role for 16+ years (see facing page).

Heiman's research employs several advanced technologies and techniques to investigate why certain types of cells in specific brain regions are particularly pivotal and vulnerable in diseases such as Huntington's disease, Parkinson's disease, schizophrenia, and addiction. Her work sits at the intersection of rapid technological advances that are accelerating discovery and a research continuum that spans fundamental neuroscience and biomedical translation.

In her new role as director, we asked Heiman to answer some big picture questions about her outlook for the field and the Institute at an exciting but also uncertain time for neuroscience.

Q: What's your take on the state of neuroscience research, both in general and at The Picower Institute?

We are making great strides at all levels, from the level of molecules and genes to neuronal circuits to whole organisms' behavior. We are at a pivotal moment where new methods and models, including AI, are accelerating discovery, allowing us to cross traditional boundaries. We used to be either "molecular," "cellular," or "systems" neuroscientists but those lines are blurring as we gain these new capabilities. What's unique about The Picower Institute is that when you consider the work here in its totality, we span all those areas. That's not often the case in research centers, but here we leverage these diverse areas of expertise that we have across our research groups to collectively better understand the brain at all levels. You can see that happening everywhere, for instance a few years back when Susumu Tonegawa, who employs molecular biology approaches to neuroscience, and Kwanghun Chung, whose work is based in chemical engineering, collaborated to map the neural traces of a memory, cell by cell, across a whole brain. It's also evident in a new study where Steven Flavell and Brady Weissbourd, who each span molecular to systems scales in different model organisms, collaborated to show how new AI tools enable us to track neural activity in live animals to achieve new insights into the connection between brain-wide neuronal activity and natural behavior (see p. 5). There's really exceptional ingenuity in our newest research group, where Linlin Fan is developing powerful light-based methods to determine exactly how brains forge connections to store and represent memories. Another example comes from Troy Littleton, who recently harnessed advanced techniques to comprehensively document how individual neurons distinguish themselves by editing their RNA.

Our ability to innovate and cross boundaries goes well beyond our own research groups, encompassing also close ties and collaborations with our exceptional colleagues here at MIT in Brain and Cognitive Sciences, in The McGovern Institute, the Biology department and the School of Engineering. Both Mriganka Sur and Elly Nedivi have made amazing advances in neural and brain imaging, for instance, in collaboration with Professor Peter So in Mechanical Engineering. Matt Wilson's lab, which has a long track record of creating open-source hardware for the neuroscience community through Open Ephys, has meanwhile been pushing other frontiers of imaging, with Ed Boyden, a Picower affiliate and professor in BCS, the McGovern Institute, and Biomedical Engineering.

Q: How are these advances improving our prospects for treating disease?

Our mission is to understand the fundamental properties of how the brain works to also improve understanding of disease. When Susumu founded the Picower as a center in 1994, this vision was almost in the realm of science fiction for some diseases. I feel great optimism that this vision will be fully achieved because new tools, collaborations, and insights are allowing us to accelerate the pace of research and discovery. We can now hope to be able to solve some of the fundamental questions regarding disease mechanisms that we posed many years ago.

In my own work, for instance studying the brain's striatum, we have been able to accelerate discoveries because of recent advances in single cell RNA sequencing and in computational analysis and machine learning. Working with Manolis Kellis in MIT's Computer Science Artificial Intelligence Lab, we've been able to much more comprehensively atlas the striatum's cell types, which not only increases our fundamental understanding of cell type diversity of this important region, but also gives us new insights into Huntington's disease, schizophrenia and also opioid use disorder. Our findings are providing the foundation for tools to perturb those cell types that seem especially vulnerable in neurodegenerative and psychiatric disease. And that's just one example, of course. Li-Huei Tsai has produced groundbreaking work to understand the changes Alzheimer's disease causes in multiple cell types in multiple regions. Her group has published many papers and insights in this area, including the very important transcriptional and epigenetic changes in microglial immune cells that contribute to Alzheimer's disease pathology.

Another great example is the highly novel work Gloria Choi has done to map the role of certain immune system signaling receptors across the brain. In a pair of studies last year, she showed how neuroimmune interactions affect social behavior, including phenotypes related to autism spectrum disorders (ASDs) and anxiety. Mark Bear has continued to break new ground in finding new treatment strategies for fragile X syndrome, an ASD, and his work holds great promise toward developing the first treatment for adults with the vision disorder amblyopia. Meanwhile, using innovative methods, a collaboration between Earl Miller, Emery Brown and BCS/McGovern colleague Ila Fiete has uncovered a potential universal signature of unconsciousness under general anesthesia that can be used to improve patient care during and after surgery (see p. 3). And Sara Prescott, who is pioneering studies of the nervous system in the airways and lungs, and Tsai Lab research scientist Ravi Raju, who is also a pediatrician, are both collaborating with Broad Institute researchers to study the biological effects that adversity and stress have on the brain and body. There are many more examples, too, where fundamental research in the Institute has led to new strategies for therapeutics, including clinical trials. Mriganka's preclinical research, for instance, helped lay the scientific groundwork for the first FDA-approved therapy for Rett syndrome.

Q: What's needed now to realize all this potential?

For 24 years we've been enormously privileged to build our research community on a foundation laid by the generosity of Barbara and Jeffry Picower in 2002, and sustained ever since by The Picower Foundation, The JPB Foundation and now its successor, the Freedom Together Foundation led by Deepak Bhargava. Susumu, Mark and Li-Huei have worked with them over the years to establish programs that, among many other things, have helped to seed fund our boldest research ideas, to support junior faculty as they approach tenure, and to support postdoctoral and graduate student trainees in their research. I can't say enough about how exceptional and important that support has been—and remains—for enabling our excellence, not just in advancing truly cutting-edge research but also for training the next generation of neuroscience leaders.

Specifically, this support has always been instrumental in helping us take our highest-risk, highest-reward ideas from conception to the point where we have enough evidence to then support the work further with federal funding, which is traditionally less tolerant of risk. Our most productive lines of research were launched by philanthropy and then developed further with government grants, typically from the National Institutes of Health.

In the last couple of years, however, the federal funding picture has become much less certain. Recently MIT President Sally Kornbluth shared what changes in federal policy have meant for MIT. With an increase in the tax on MIT's endowment and ongoing changes in how federal science funding is spent—even when fully allocated by Congress—federal research awards at MIT have dropped by 20 percent this year. The fiscal year is not over quite yet, but as of now, there have been noticeably fewer new federal grants to Picower Institute labs. Across MIT, including The Picower Institute and our affiliated academic departments such as BCS, these changes not only stand to reduce research volume, but also our ability to bring on graduate students who represent the future of the field.

In this new climate, we are beginning to think differently about what "public" support means. Every family is touched in some way by developmental, psychiatric, neurological, or neurodegenerative disease, and all of us share a fascination with how the brain enables us to think, learn, create, remember, and connect with one another. By investing in neuroscience research, supporters can play a direct role in advancing discoveries that have the potential to improve countless lives. By supporting our work and our scientists directly, individual donors are now poised to become even more essential contributors to the solutions to some of the most compelling mysteries and the most urgent challenges of neuroscience.

We have never had better approaches and tools to understand the brain and never had a greater opportunity to translate discovery into benefits for human health. The questions are still enormous, but for the first time many of them feel within reach of being solved.

Myriam Heiman in the 6th floor "reading terrace" of MIT's Building 46. *Photos by Steph Stevens.*

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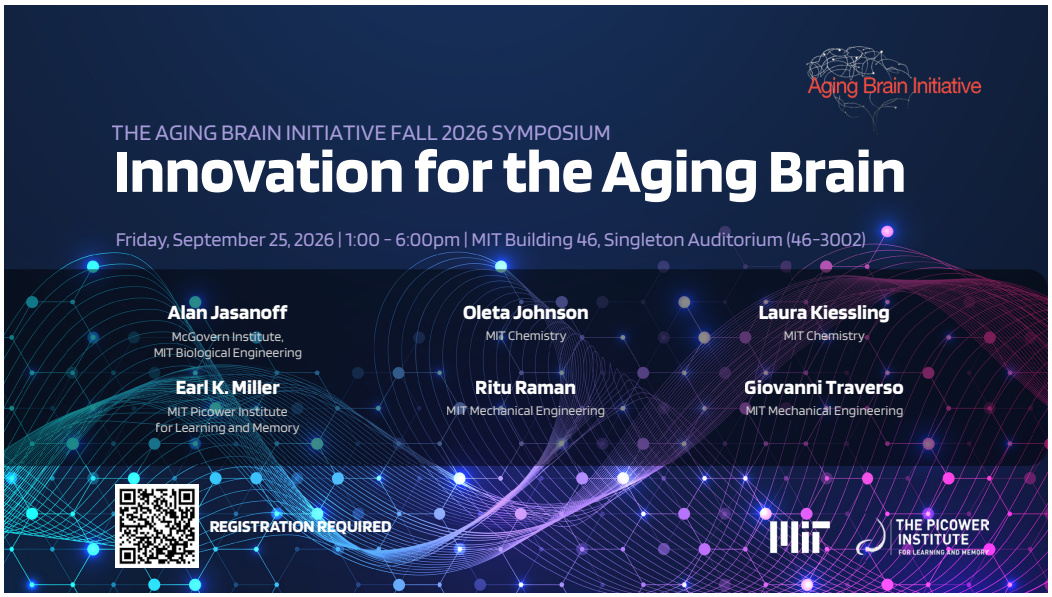

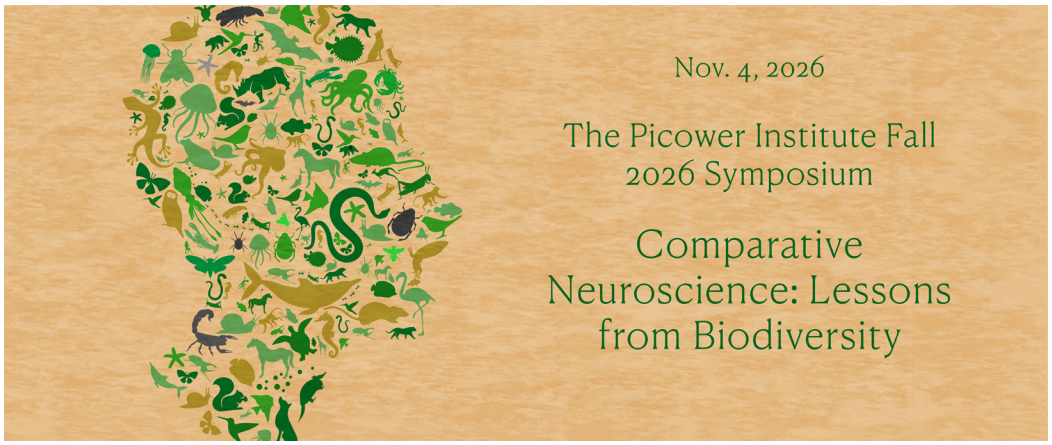

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OUR VISION

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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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; **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