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Neuroscience News

SUMMER 2025

THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY

DIRECTOR'S **MESSAGE**

Dear Friends,

In a video commemorating our 20th Anniversary in 2022, Picower Institute founding director Susumu Tonegawa said this about scientific research: "As long as you are interested in a very fundamental problem, history has shown it is useful."

What did he mean by that? A lot of research is directed toward achieving a specific and practical result, for instance a new drug. But science driven by basic curiosity can be just as sure a path to a relevant and important impact in medicine as a head-on, pragmatic approach. Time and again we've seen some of the most important insights into brain disease emerge from neuroscience that didn't begin with the intention to achieve that result. And much of the feedstock of applied research at pharma companies is the product of basic insights from curiosity-driven university research.

Our cover story on autism research (p. 8) illustrates this point. Mark Bear didn't set out to bring promising autism drugs to clinical trials, but his fundamental research on how neural connections weaken led him there. Mriganka Sur didn't expect to lay the groundwork for the first-ever FDA-approved treatment for Rett syndrome, but the opportunity arose from his basic curiosity about a protein that helps neural connections mature. Gloria Choi's work to explain connections between infection and autism was intentional from the start, but it was motivated by her fundamental interest in the relationship between the immune and central nervous systems.

Our news stories illustrate this, too. Gloria's work has now also revealed relevance to anxiety (p. 3). Susumu's longstanding curiosity about the molecular biology of memory has yielded a new insight into PTSD (p. 5). And while my lab has been quite intentional in testing gamma-frequency sensory stimulation to treat Alzheimer's disease and Down syndrome (p. 4), I note that when my lab first stimulated gamma brain rhythms in 2009, we had no idea it would produce a potential therapy now in clinical trials. We just wanted to try out a then-new technology, not knowing where it would lead.

Let's never lose sight of the value of curiosity-driven science.

LI-HUEI TSAI, DIRECTOR

The Picower Institute for Learning and Memory

In kids, EEG monitoring of consciousness **safely reduces** anesthetic use

A randomized, controlled clinical trial in Japan among more than 170 children aged 1 to 6, shows that by using EEG readings of brain waves to monitor unconsciousness, an anesthesiologist can significantly reduce the amount of the anesthesia administered to safely induce and sustain each patient's anesthetized state. On average the little patients experienced significant improvements in several post-surgical outcomes, including quicker recovery and reduced incidence of delirium.

"I think the main takeaway is that in kids, using the EEG, we can reduce the amount of anesthesia we give them and maintain the same level of unconsciousness," said study co-author Emery N. Brown, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience at MIT and an anesthesiologist at Massachusetts General Hospital.

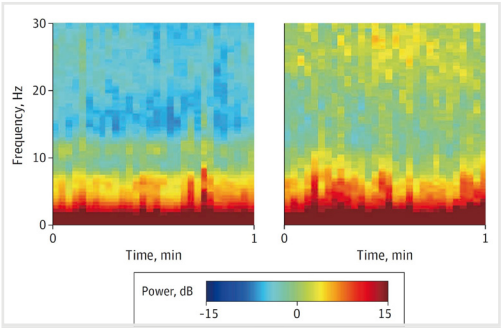
Yasuko Nagasaka, chair of anesthesiology at Tokyo Women's Medical University and a former colleague of Brown's in the United States, designed the study published in *JAMA Pediatrics*. She asked Brown to train and advise lead author Kiyoyuki Miyasaka of St. Luke's International Hospital in Tokyo on how to use EEG to monitor unconsciousness and adjust anesthesia dosing in children. Miyasaka then served as the anesthesiologist for all patients in the trial.

Brown's research has shown that a person's level of consciousness under any particular anesthetic drug is discernible from patterns of their brain waves. Each child's brain waves were measured with EEG, but in the control group Miyasaka adhered to standard anesthesia dosing protocols while in the experimental group he used the EEG measures as a guide for dosing. When he used EEG, he was able to induce the desired level of unconsciousness with a concentration of 2 percent sevoflurane gas, rather than the standard 5 percent. Maintenance of unconsciousness, meanwhile, only turned out to require 0.9 percent concentration, rather than the standard 2.5 percent.

Meanwhile, a separate researcher, blinded to whether EEG or standard protocols were used, assessed the kids for "pediatric anesthesia emergence delirium" (PAED), in which children sometimes wake up from anesthesia with a set of side effects including lack of eye contact, inconsolability, unawareness of surroundings, restlessness and non-purposeful movements. Children who received standard anesthesia dosing met the threshold for PAED in 35 percent of cases (30 out of 86), while children who received EEG-guided dosing met the threshold in 21 percent of cases (19 out of 91).

Meanwhile, the authors reported that on average EEG-guided patients had breathing tubes removed 3.3 minutes earlier, emerged from anesthesia 21.4 minutes earlier, and were discharged from post-acute care 16.5 minutes earlier than patients who received anesthesia according to the standard protocol.

The authors noted that the quicker recovery among patients who received EEG-guided anesthesia was not only better medically, but also reduced healthcare costs. Time in post-acute care in the U.S. costs about $46 a minute so the average reduced time of 16.5 minutes would save about $750 per case.



Children who experienced PAED (right) showed higher power at several frequencies up to 30Hz than children who did not experience PAED (left).

In the study the authors also present comparisons of the EEG recordings from children in the control and experimental groups. There are notable differences in the "spectrograms" that charted the power of individual brain wave frequencies both as children were undergoing surgery and while they were approaching emergence from anesthesia, Brown said.

The findings further validate the idea that monitoring brain waves during surgery can provide anesthesiologists with actionable guidance to improve patient care, Brown said. Training in reading EEGs and guiding dosing can readily be integrated in the continuing medical education practices of hospitals, he added.

Immune cytokines act on the brain, inducing **anxiety or sociability**

A growing body of evidence suggests that some immune system signaling molecules, or cytokines, can influence the brain, leading to behavioral changes during illness.

In two new studies from MIT and Harvard Medical School, focused on a cytokine called IL-17, researchers found that IL-17 acts on two distinct brain regions — the amygdala and the somatosensory cortex — to exert two divergent effects. In the amygdala, IL-17 can elicit feelings of anxiety, while in the cortex it promotes sociable behavior.

These findings suggest that the immune and nervous systems are tightly interconnected, said Gloria Choi, an associate professor in The Picower Institute, and one of the senior authors of the studies in *Cell*.

"If you're sick, there's so many more things that are happening to your internal states, your mood, and your behavioral states, and that's not simply you being fatigued physically. It has something to do with the brain," Choi said.

Jun Huh, an associate professor of immunology at Harvard Medical School, is also a senior author of both studies. One of the papers was led by Picower Institute Research Scientist Byeongjun Lee and former Picower Institute research scientist Jeong-Tae Kwon, and the other was led by Harvard Medical School postdoc Yunjin Lee and Picower Institute postdoc Tomoe Ishikawa.

Several years ago, Choi and Huh found that IL-17 was involved in a phenomenon known as the "fever effect." Large-scale studies of autistic children have found that social behavior symptoms sometimes temporarily improve when they have an infection. In a 2019 study in mice, Choi and Huh showed that in some cases of infection, IL-17 is released and suppresses a small region of the brain's cortex known as S1DZ, counteracting overactivation of neurons in this region that can lead to autism-like behavioral symptoms, including repetitive behaviors and reduced sociability.

IL-17 comes in six different forms, and there are five different receptors that can bind to it. In their two new papers, the researchers set out to map which of these receptors are expressed in different parts of the brain. This mapping revealed that a pair of receptors known as IL-17RA and IL-17RB is found in the cortex, including in the S1DZ region. The receptors are located in a population of neurons that receive proprioceptive input and are involved in controlling social behavior.

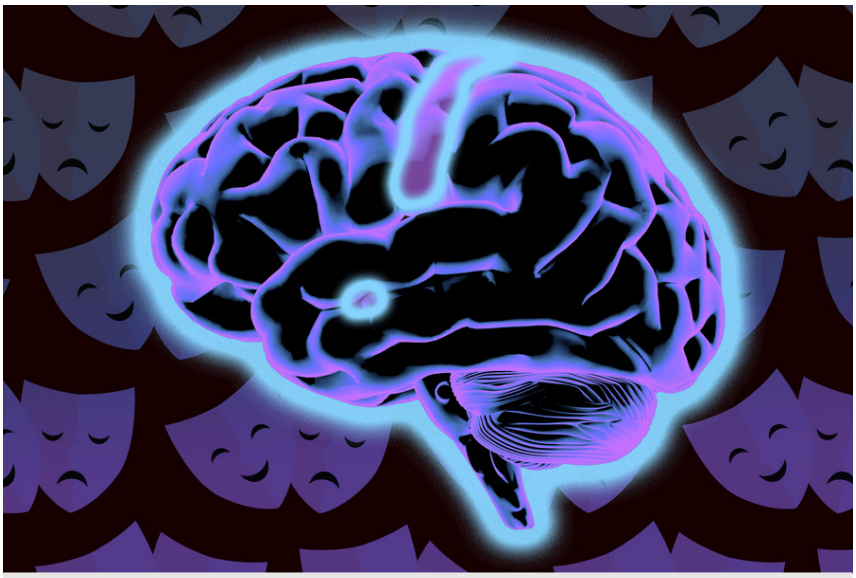
When a type of IL-17 known as IL-17E binds to these receptors, the neurons become less excitable, which leads to the behavioral effects seen in the 2019 study.

"IL-17E, which we've shown to be necessary for behavioral mitigation, actually does act almost exactly like a neuromodulator in that it will immediately reduce these neurons' excitability," Choi says.

Choi hypothesizes that IL-17 may have originally evolved as a neuromodulator, and later on was appropriated by the immune system to play a role in promoting inflammation. Indeed, IL-17E is actually made by neurons in the cortex, including S1DZ.

In the other *Cell* paper, the researchers explored another brain location where they found IL-17 receptors — the amygdala. This almond-shaped structure plays an important role in processing emotions, including fear and anxiety.

That study revealed that in a region known as the basolateral amygdala (BLA), the IL-17RA and IL-17RE receptors, which work as a pair, are expressed in a discrete population of neurons. When these receptors bind to IL-17A and IL-17C, the neurons become more excitable, leading to an increase in anxiety.



An illustration highlights regions affected by cytokines: A region of the cortex (vertical strip) and the amygdala (small circle).

The researchers also found that, counterintuitively, if animals are treated with antibodies that block IL-17 receptors in the body, that actually increases the amount of IL-17C that can reach the brain. This finding may help to explain why a clinical trial of a drug targeting the IL-17-RA receptor for psoriasis treatment led to unexpected problems with mental health.

During infections, some degree of anxiety may be beneficial, keeping sick individuals away from others to whom the infection could spread, Choi hypothesizes.

"Other than its main function of fighting pathogens, one of the ways that the immune system works is to control the host behavior, to protect the host itself and also protect the community the host belongs to," she says. "One of the ways the immune system is doing that is to use cytokines, secreted factors, to go to the brain as communication tools."

The researchers found that the same BLA neurons that have receptors for IL-17 also have receptors for IL-10, a cytokine that suppresses inflammation. This molecule counteracts the excitability generated by IL-17, giving the body a way to shut off anxiety once it's no longer useful.

Together, the two studies suggest that the immune system, and even a single family of cytokines, can exert a variety of effects in the brain.

In **Down syndrome** mice, 40Hz light and sound improve cognition, neurogenesis, connectivity

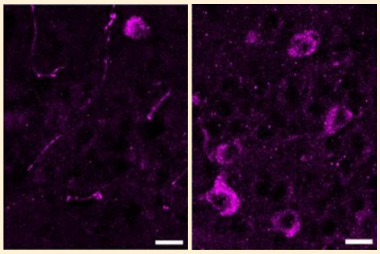
Researchers at The Picower Institute and the Alana Down Syndrome Center found that 40Hz sensory stimulation improved cognition and circuit connectivity and encouraged the growth of new neurons in mice genetically engineered to model Down syndrome.

Li-Huei Tsai, Picower Professor and senior author of the study in *PLOS One*, said that the results are encouraging but also cautioned that more work is needed to test whether the method could provide clinical benefits for people with Down syndrome. Her lab has begun a small study with human volunteers at MIT.

"While this work, for the first time, shows beneficial effects on Down syndrome using an imperfect mouse model, we need to be cautious as there is not yet data showing whether this also works in humans," said Tsai, who directs The Picower Institute and The Alana Center.

Still, she said, the newly published article adds evidence that 40Hz light and sound stimulation can promote a broad-based, restorative, "homeostatic" health response in the brain amid a wide variety of pathologies. Most 40Hz studies have addressed Alzheimer's disease in humans or mice, but others have found benefits from the stimulation for conditions such as "chemo brain," and stroke.

In the study, the research team led by postdoc Md Rezaul Islam and former graduate student Brennan Jackson worked with the commonly used "Ts65Dn" Down syndrome mouse model. Their experiments showed that an hour a day of 40Hz light and sound exposure for three weeks was associated with significant improvements on three standard short-term memory tests. Stimulated mice exhibited significantly more connections among neurons in the hippocampus (a key memory region) and produced more new neurons, a phenomenon called "neurogenesis."



Magenta staining reveals more neurons expressing the protective protein Reelin in mice that received 40Hz stimulation (right) than those that did not (left).

An analysis of gene expression also yielded other key insights relevant to the significant risk of developing Alzheimer's disease that people with Down syndrome face. One is that a cluster of genes whose expression typically declines with normal aging and in Alzheimer's disease, remained at higher expression levels among mice who received 40Hz sensory stimulation. And the researchers also found evidence that mice that received stimulation retained more cells in the hippocampus that express Reelin. Reelin-expressing neurons are especially vulnerable in Alzheimer's disease, but expression of the protein is associated with cognitive resilience amid Alzheimer's disease pathology, which Ts65Dn mice develop.

Evidence expanding that 40Hz sensory stimulation promotes brain health

A decade after scientists in The Picower Institute first began testing whether sensory stimulation of the brain's 40Hz "gamma" frequency rhythms could treat Alzheimer's disease in mice, a growing evidence base supporting the idea that it can improve brain health—in humans as well as animals—has emerged from the work of labs all over the world. A new review article in *PLOS Biology* describes the state of research so far.

"People have used many different ways to induce gamma including sensory stimulation, transcranial alternating current stimulation or transcranial magnetic stimulation, but the key is delivering stimulation at 40 Hz. They all see beneficial effects," said Li-Huei Tsai, Picower Professor at MIT, director of MIT's Aging Brain Initiative, and senior author of the new review with postdoc Jung Park.

Li-Huei Tsai delivers a February lecture at MIT on her 40Hz research

Starting with a paper in 2016, a collaboration led by Tsai has produced a series of studies showing that 40Hz stimulation via light, sound, the two combined, or tactile vibration reduces hallmarks of Alzheimer's pathology such as amyloid and tau proteins, prevents neuron death, decreases synapse loss, and sustains memory and cognition in various Alzheimer's mouse models. The collaboration's investigations of the underlying mechanisms has identified specific cellular and molecular responses in many brain cell types including neurons, microglia, astrocytes, oligodendrocytes and the brain's blood vessels. Last year, the lab reported that 40Hz audio and visual stimulation induced interneurons in mice to increase release of the peptide VIP, prompting increased clearance of amyloid from brain tissue via the brain's glymphatic "plumbing" system.

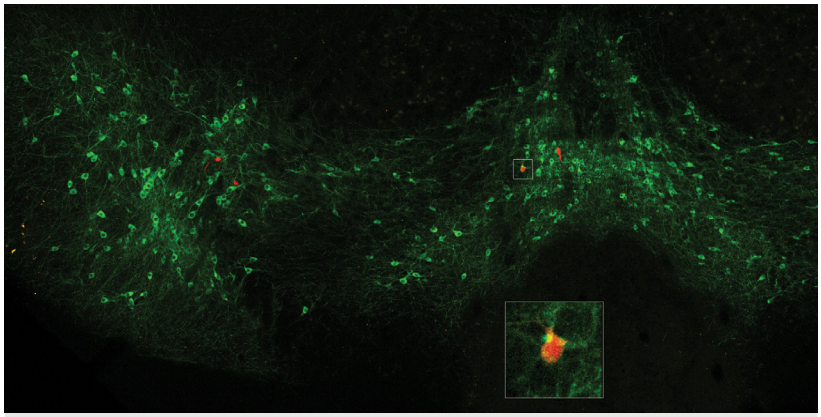
Meanwhile, at MIT and at the MIT spinoff company Cognito Therapeutics, phase II clinical studies have shown that people with Alzheimer's exposed to 40Hz light and sound experienced a significant slowing of brain atrophy and improvements on some cognitive measures compared to untreated controls. Cognito, which has also measured significant preservation of the brain's "white matter" in volunteers, has been conducting a pivotal, nationwide phase III clinical trial of sensory gamma stimulation for more than a year.

Many other labs have produced studies adding to the evidence. In 2024 a research team in China independently corroborated that 40Hz sensory stimulation increases glymphatic fluid flows in mice. A Harvard Medical School-based team in 2022 showed that 40Hz gamma stimulation using Transcranial Alternating Current Stimulation significantly reduced the burden of tau in three out of four human volunteers. And in another study involving more than 100 people, researchers in Scotland in 2023 used audio and visual gamma stimulation (at 37.5 Hz) to improve memory recall.

Dopamine signals when a **fear** can be forgotten

A new study in mice by MIT neuroscientists shows that release of dopamine via a specific interregional brain circuit provides the "all-clear" signal when a danger has passed and fear can be extinguished. The research therefore pinpoints a potentially critical mechanism of mental health, restoring calm when it works, but prolonging anxiety or even post-traumatic stress disorder when it doesn't.

"Dopamine is essential to initiate fear extinction," said Michele Pignatelli di Spinazzola, co-author of the new study from the lab of senior author Susumu Tonegawa, Picower Professor of biology and neuroscience at the RIKEN-MIT Laboratory for Neural Circuit Genetics in The Picower Institute for Learning and Memory and an HHMI Investigator.



An edited version of a figure from the research shows the ventral tegmental area, highlighting dopamine-associated neurons in green and one that connects to the posterior amygdala (magnified in inset) in red.

In 2020 Tonegawa's lab showed that learning to be afraid, and then learning when that's no longer necessary, result from a competition between populations of cells in the brain's amygdala region. When a mouse learns that a place is "dangerous" (because it gets a little foot shock there), the fear memory is encoded by neurons in the anterior of the basolateral amygdala (aBLA) that express the gene Rspo2. When the mouse then learns that a place is no longer associated with danger (because they wait there and the zap doesn't recur), neurons in the posterior basolateral amygdala (pBLA) that express the gene Ppp1r1b encode a new fear extinction memory that overcomes the original dread. Notably those same neurons encode feelings of reward, helping to explain why it feels so good when we realize that an expected danger has dwindled.

In the new study, the lab, led by former members Xiangyu Zhang and Katelyn Flick, sought to determine what prompts these amygdala neurons to encode these memories. The rigorous set of experiments the team reports in the *Proceedings of the National Academy of Sciences* show that it's dopamine sent to the different amygdala populations from distinct groups of neurons in the ventral tegmental area (VTA).

"Our study uncovers a precise mechanism by which dopamine helps the brain unlearn fear," said Zhang, who also led the 2020 study. "We found that dopamine activates specific amygdala neurons tied to reward, which in turn drive fear extinction. We now see that unlearning fear isn't just about suppressing it—it's a positive learning process powered by the brain's reward machinery. This opens up new avenues for understanding and potentially treating fear-related disorders like PTSD."

The team ran several experiments using several methods to causally establish dopamine as the fear extinction signal.

Nervous system's surprising flexibility evident in animal's infection response

Whether you are a person about town or a worm in a dish, life can throw all kinds of circumstances your way. What you need is a nervous system flexible enough to cope. In a new study, MIT neuroscientists show how even a simple animal can switch many gears in its brain to muster an adaptive response to an infection.

When *C. elegans* worms fed on infectious *Pseudomonas* bacteria that made them sick (as it does to humans), they responded similarly to many animals including people. They ate less and became more lethargic. When the researchers looked across the nervous system to see how that sickness behavior happened, they discovered that the worms had completely revamped the roles of several of its 302 neurons and some of the peptides they secrete across the brain to modulate behavior. Systems that responded to stress in one case or satiety in another became reconfigured to cope with the infection.

"This is a question of how do you adapt to your environment with the highest level of flexibility given the set of neurons and neuromodulators you have," said postdoc Sreeparna Pradhan, co-lead author of the new study in *Nature Communications*. "How do you make the maximum set of options available to you."

The research to find out took place in the lab of senior author Steve Flavell, associate professor in The Picower Institute and an investigator of the Howard Hughes Medical Institute. Former Flavell lab graduate student Gurrein Madan co-led the research.

Pradhan said the team discovered several surprises in the course of the study including that a neuropeptide called FLP-13 completely flipped its function in infected animals versus animals experiencing other forms of stress. Previous research had shown that when worms are stressed by heat, a neuron called ALA releases FLP-13 to cause the worms to go into quiescence, a sleep-like state. But when the worms in the new study ate *Pseudomonas* bacteria and got sick, a band of other neurons released FLP-13 to fight off quiescence, enabling the worms to survive longer. Meanwhile, ALA took on a completely different role during sickness: leading the charge to suppress feeding by emitting a different group of peptides.

Gloria Choi earns Samsung Ho-Am Prize for Medicine

Honor recognizes Choi's research on connections between the immune and central nervous systems and their relevance to autism and other disorders.

The Ho-Am Foundation has selected Gloria Choi, Associate Professor in The Picower Institute for Learning and Memory and the Department of Brain and Cognitive Sciences at MIT, to receive the 2025 Samsung Ho-Am Prize for Medicine.

Choi's research focuses on neuroimmunology, the study of the bilateral communication between the immune and central nervous systems. While scientists once thought the brain remained walled off from the body's immune system activity, numerous studies, including from Choi's lab and that of her frequent collaborator Jun Huh at Harvard Medical School, have shown that there is robust cross-talk with profound effects. For instance, in a series of papers starting in 2016, Choi's collaboration has produced in mice an explanation for two clinically documented mysteries involving patients with autism spectrum disorders.

One mystery is the observation that infection during pregnancy seems to increase the risk for autism in offspring. Choi's research showed that amid certain maternal microbiome conditions, infection can spur immune cells to produce an excess of the cytokine IL-17A. When the cytokine reaches the brain of the fetus, it alters development in a specific region of the cortex leading to increased neural activity in circuits affecting social behavior. Another mystery was why certain symptoms appear to improve when some people with autism contract an infection. Choi and Huh's research showed that in mice modeling autism, either by maternal infection or certain genetic mutations, increased production of IL-17A calmed excessive neural activity in the same region of the cortex.

"[Choi] is a leading neuroscientist who has made groundbreaking contributions to our understanding of neurodevelopmental disorders," the Korea-based foundation said in an April 2 announcement. "Through research using animal models, she uncovered a critical link between the immune system and brain health. Her findings reveal that, while excessive activation of the immune system during pregnancy can disrupt normal brain development, the immune system can also be harnessed to help alleviate autism symptoms. Dr. Choi's ongoing work to unravel the complex interactions between the nervous and immune

systems holds great promise for the development of novel strategies to prevent and treat disorders such as autism, depression, and dementia."

Choi has also examined neuroimmune effects on social behavior in other ways. In a study in 2021 she demonstrated that male mice, upon detecting an olfactory indicator of illness in female mice, would suppress their instinct to mate: a form of social distancing. In her most recent work, Choi has been mapping immune system cytokine receptors across the whole mouse brain. That information has enabled her to make new discoveries that not only further explain the effects of cytokines on social behavior during development, but also a mechanism by which different cytokines can ether trigger or reduce anxiety (see p. 3).

Choi said she is grateful for the Ho-Am Foundation's recognition of and support for her work.

"I am deeply honored to receive the Ho-Am Prize," Choi said. "This recognition not only affirms the importance of exploring the dialogue between the immune and nervous systems but also encourages our continued efforts to better understand and ultimately treat complex brain disorders. I am grateful to the Ho-Am Foundation for supporting this line of research."

Picower people earn School of Science 'Infinite' honors

Each year MIT's School of Science honors research staff with Infinite Mile (general) and Infinite Kilometer (scientific staff only) awards (a play on MIT's Infinite Corridor) to recognize those who go above and beyond.

This year Mandana Sassanfar, who directs outreach programs in the departments of biology, brain and cognitive sciences, the Center for Brains, Minds & Machines, and The Picower Institute for Learning and Memory, won an Infinite Mile for her work. "She forges deep and lasting, uncommonly supportive, and inspiring relationships with students that have helped to launch numerous successful scientific careers, including faculty members around the globe and two in the Department of Biology," her nominators noted. "Her outreach has brought scores of brilliant minds into the MIT graduate student community."

Infinite Kilomter winner Hiroki Sugihara, a research scientist in The Picower Institute for Learning and Memory, was nominated by Mriganka Sur, who wrote, "Hiroki is an indispensable member of our lab, who works selflessly to make the lab productive and efficient."

With Searle Scholar award, Fan will study serotonin role in memory

Assistant Professor Linlin Fan will apply her lab's precise "all-optical" techniques to study how serotonin might influence plasticity in memory, and whether psychedelics affect that.

There is a paradox in the brain's role as a memory making organ: It has to be flexible, or "plastic," enough to incorporate new information yet stable enough to keep the information it stores enduringly available. With a new Searle Scholar Award, MIT neuroscientist Linlin Fan will launch a study to determine how the neuromodulatory chemical serotonin may help the brain overcome the challenge.

The Searle Scholars program has supported high-risk, high-reward research among early career faculty members in the biomedical sciences and chemistry. This year the program chose 15 scholars including Fan, Assistant Professor in The Picower Institute for Learning and Memory and the Department of Brain and Cognitive Sciences, to receive a total of $300,000 over three years in flexible funding for their work.

"We are interested in studying brain-state-dependent plasticity rules, and serotonin can powerfully modulate brain states," Fan said.

Signs of serotonin's influence on memory encoding have been hard to measure in mice with enough precision to study and establish as a causal influence, especially during a live behavior like navigating and learning a new space. But Fan's lab specializes in advanced optical techniques that can simultaneously use light both to finely control and sensitively measure the subtleties of electrical and neuromodulatory chemical activity that govern neuronal plasticity. In a study she co-led last year, for example, Fan and her collaborators used her all-optical physiology methods and a method for tracking an endocannabinoid neuromodulator to understand how "place cell" neurons in the hippocampus squelched an inhibitory signal from another neuron when it was time to refine a memory of a location.

Among the notable aspects of the 2024 study was that the memory mechanism they characterized involving endocannabinoid receptors could potentially be disrupted by cannabinoid drugs such as marijuana. In the new study, Fan plans to examine how the serotonin-based plasticity rules at play might be affected by psychedelic drugs that act on serotonin systems in the brain.

Fan said she is honored to have the Searle Scholars program's support, which is funded through the Searle Funds at The Chicago Community Trust and administered by Kinship Foundation.

"I am very grateful for the support from the Kinship Foundation, and I am appreciative to be selected as a Searle Scholar among so many great scientists," Fan said.

Congratulations new **PhDs**

Six graduate students have earned their doctorates in Picower labs so far this spring with more defenses yet to come:

- **Dr. Audrey Effenberger**, Heiman Lab, "Oligodendrocyte progenitor heterogeneity in normal aging and neurodegeneration"
- **Dr. Talya Kramer**, Flavell Lab, "Neural Sequences Underlying Directed Turning in *C. elegans*"
- **Dr. Madison Leet**, Bear Lab, "Investigating the prevalence and mechanisms of recovery from amblyopia after monocular vision loss"
- **Dr. Alex Lenail**, Heiman Lab, "Transcriptional Reprogramming to Reverse Aging-Associated Transcriptional Dysregulation in Neurons"
- **Dr. Francis Reilly-Andújar**, Bear Lab, "Non-invasive tuning of experience-dependent plasticity in the primary visual cortex"
- **Dr. Bee Sathitloetsakun**, Heiman Lab, "Investigating the Roles of Scn4b in Huntington's Disease Pathogenesis"

BCS honors faculty, staff, student

We're proud of Picower Institute members who earned Brain and Cognitive Science Department awards this spring.

Faculty honors went to Professors Matt Wilson (for undergrad advising), Earl Miller (grad student mentoring), Gloria Choi (undergrad teaching), and Troy Littleton (community impact). Graduate student Audrey Effenberger earned an award for undergrad teaching.

Among research and administrative staff, awards went to "Go-To Person" Taylor Johns, "Morale Boosters" Brittany Greenough and Alex Sokhina, and "Problem Solvers" Arek Hamalian and Eleana MacPhail.

Matt Wilson, Earl Miller and Gloria Choi. *Photo by Jarret Bencks.*

Autism advances

Rooted in fundamental curiosity about how the brain works, Picower scientists continue to break new ground in understanding autism and devising treatment strategies.

None of the faculty members in The Picower Institute is an "autism researcher," but The Institute has been advancing research on autism spectrum disorders for nearly 20 years. Five labs are doing autism research right now. How can this be? Picower Institute scientists seek to discover the fundamental mechanisms that make the brain work. That turns out to be a fruitful—and maybe essential—way to improve understanding of how it sometimes works differently.

"You can't solve a brain disorder by just studying the disorder," said Newton Professor Mriganka Sur, a Picower Institute faculty member who directs MIT's Simons Center for the Social Brain, a major hub for Boston-area autism research. "It will be difficult to understand the disorder unless that understanding is built on a lot of basic biology."

It's not a simple challenge. The autism spectrum includes conditions that produce severe intellectual disabilities and others that produce behavioral differences that advocates say merely need to be recognized, rather than medicalized, Sur said. What unifies the spectrum are difficulties with social behavior, restricted interests, and repetitive behaviors. The U.S. Centers for Disease Control estimates that 1 in 31 American eight-year-olds had an autism diagnosis in 2022.

The causes of ASDs are also complex. About 30 years ago scientists began tracing some profound ASDs, such as Fragile X syndrome, directly to single genes. They have since accumulated evidence associating hundreds of genes with increasing likelihood of autism. Some non-genetic, or "environmental," factors, such as maternal infection during fetal development, also play a role.

Given the complexities, research must incorporate many perspectives and scales, ranging from the molecules that help neurons communicate via "synapse" connections to the cognition produced by the coordinated neural activity of millions of cells. That's part of what has made MIT's brain science community, and in particular The Picower Institute for Learning and Memory, such a productive contributor to the global autism research enterprise, said Sur who also led MIT's Department of Brain and Cognitive Sciences from 1997 to 2012.

"The disorder manifests all the way from genes, proteins and synapses, to circuits and behavior," he said. "This is the place where we have built a department and these centers that study the brain and mind across so many levels of analysis where autism should be studied."

Indeed, among the updates below on autism research projects in five Picower labs, each is deeply rooted in a history of fundamental curiosity about brain function. Taken together, the investigations span scales from subcellular structures to wide brain networks.

Connections from connections

Picower Professor Mark Bear's autism research began with his discovery of molecular mechanisms by which synaptic connections can weaken, a process called "long-term synaptic depression" (LTD). In one mechanism, the neurotransmitter glutamate activates a neural receptor called mGluR5, spurring protein synthesis at the synapse. When Bear learned that the protein missing in fragile X syndrome—called FMRP—restrains protein synthesis, he realized that a potential source of the syndrome's neurological symptoms could be exaggerated responses to mGluR5 activation. Bear hypothesized that inhibiting protein synthesis at the synapse could be a fragile X treatment strategy.

"I spent a lot of time thinking about the scientific risk of shifting my focus to fragile X," Bear said. "But the possibility was so exhilarating that we might be able to help kids with fragile X, I decided to jump in with both feet."

In 2007 his lab showed that genetically knocking down mGluR5 activity significantly improved many symptoms for fragile X mice. In succeeding years, Bear and collaborators sought out, identified and tested several drugs that could inhibit signaling by mGluR5, including in phase II and III clinical trials. His lab also discovered that the mGluR5 pathway mattered not only in fragile X, but also several other ASDs.

In 2011, for instance, his lab showed that mGluR5-related protein synthesis engaged in a molecular tug-of-war with another protein synthesis process driven by other receptors. If the balance moved too far in one way, it led to fragile X, if it went the other way, it led to another ASD: Tuberous Sclerosis (TSC). In a new paper this past February, Bear's lab discovered a receptor that, when activated, could restore the balance to treat Fragile X mice. The study also implied (but didn't test) that reducing activation of the receptor might restore the balance in TSC mice.

> **You can't solve a brain disorder by just studying the disorder. It will be difficult to understand the disorder unless that understanding is built on a lot of basic biology."**
>
> **–Mriganka Sur**

Meanwhile, Bear identified another drug to treat fragile X, called arbaclofen, that acts to suppress glutamate release. Studies in two mouse models of genetically defined causes of autism, fragile X and chromosome 16p11.2 microdeletion, yielded promising results. He founded a company, Seaside Therapeutics, to run clinical trials in fragile X. The phase 2 and phase 3 studies yielded similarly poignant results: encouraging benefits but near misses of the main behavioral endpoints needed for FDA approvals.

Clinical trial variables such as dose and treatment duration, patient ages and outcome measures, are difficult to guess in advance, and the company ran out of funding to continue. However, many of the lessons from this early work were applied in recent academic trials of arbaclofen in Europe and Canada in patients with ASDs of unknown cause, and the results suggest a broad benefit in social function Bear said. To raise the investment needed to launch a new U.S. trial, he has formed a new company, Allos Pharmaceuticals.

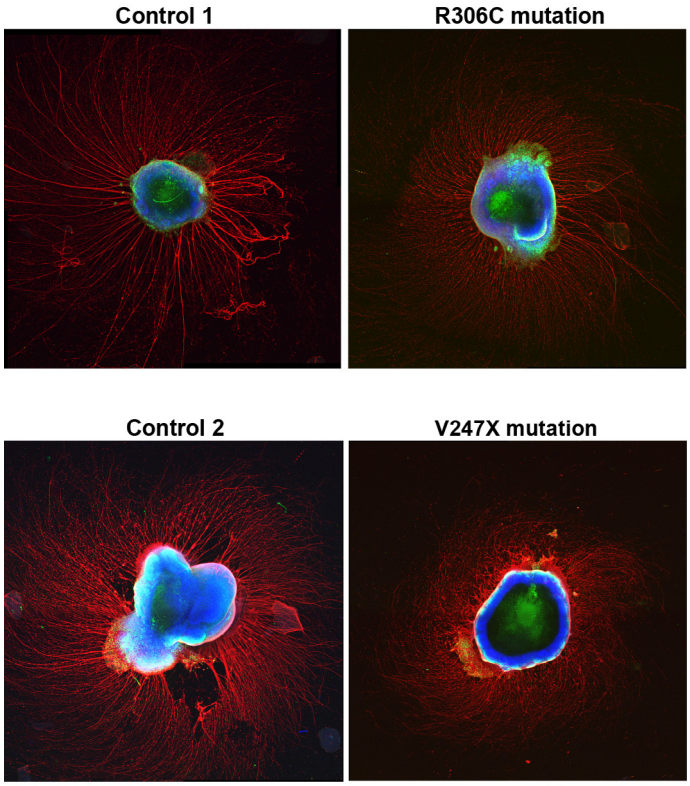
And in the lab, postdoc and former graduate student Sara Kornfeld-Sylla is studying a potential new way to personalize treatment for fragile X patients. She has documented in both mice and humans atypical brain wave patterns that vary by individual. Kornfeld-Sylla's research suggests that the signatures could be used as a non-invasive readout to guide how much medicine an individual needs.

Down the hall from Bear's lab in The Picower Institute is that of Menicon Professor Troy Littleton, whose lab works with fruit flies to study the fundamental protein machinery that enables synapses to form, function and change. Back in 2013 Littleton joined a three-lab Simons Center "targeted project" to investigate how mutations in a gene called Shank3 lead to ASD pathophysiology and to identify treatments. In a 2016 paper, Littleton's lab showed that the Shank3 protein is necessary for the receiving side of a synaptic connection to incorporate signaling receptors needed for proper formation and maturation. With an eye on a therapeutic strategy, the study demonstrated ways to rescue synapse development.

Now Littleton's lab has embarked on another autism project. Postdoc Chhavi Sood, a Simons Center Fellow, is looking at a different function of FMRP than Bear's lab. Her studies focus on a possible role in regulating how proteins are trafficked within neurons to create channels for importing calcium and exporting potassium ions. Those electrochemical dynamics affect how often a cell releases neurotransmitters across a synapse. In fragile X, neurons are too active and Sood's experiments examining how FMRP mutations affect ion channels have begun to identify clues as to why.

A center and a treatment

When Sur founded the Simons Center in 2012, his goal with the Simons Foundation Autism Research Initiative was to support such projects: multi-lab investigations of major themes and enterprising new ideas among young fellows. Over the last 13 years, the center has not only involved virtually every Picower Institute lab, but also 16 institutions around Boston, yielding more than 400 peer-reviewed papers.



Structural features such as neural axon growth or migration differed significantly in 3D human brain tissue cultures made with different Rett syndrome mutations. *Image courtesy: Tatsuya Osaki.*

Sur's own research has illuminated several aspects of autism. He has been part of a multi-lab project to evaluate whether marmosets, a small but highly social primate, might be a uniquely informative model organism for autism studies. In a paper earlier this year his lab showed that they make certain predictions much like humans do, which is important because prediction is a cognitive function known to differ in ASDs.

Sur has led pioneering research on an autism-related disorder, Rett syndrome, that originated from his studies of synapses. Caused by mutations in the gene MeCP2, Rett syndrome leads not only to autism symptoms but devastating intellectual, motor and other disabilities. When Sur's lab in 2006 was studying synaptic proteins, his team found that a protein called IGF-1 was needed for synapses to mature. Based on a 2007 paper that showed that shutting down the MeCP2 gene made mice sick, but even adolescent mice recovered when the gene was turned on, Sur inferred that in Rett syndrome, synapses remain immature but can be induced to mature. Eager to use his insight for impact, he obtained mice modeling Rett syndrome from an MIT colleague and gave them doses of an IGF-1 peptide. In a 2009 study, Sur's team reported that treated Rett mice improved markedly. His study caught the attention of a company that had an IGF-1 peptide, but hadn't known to try it with Rett patients. That company went on to conduct successful clinical trials leading to the first-ever FDA-approved Rett syndrome treatment in 2023.

(Continued on next page)

Sur has continued to publish studies revealing how MeCP2 mutations disrupt brain development. A 2017 study found that mutations can lead to misregulation of micro RNAs that in turn hinders the birth of new neurons. Using advanced microscopy techniques, Sur's lab has also shown that newborn human neurons have trouble migrating to their correct positions in 3D brain tissue cultures. In a new study, online as a preprint, Sur's lab extends that work by examining neural activity in the 3D cultures. They document how two specific MeCP2 mutations each alter the structure, gene expression and neural activity patterns in the cultures. They show that for each mutation, they could rescue the observed dysfunction the lab. Notably, the used baclofen (related to arbaclofen) for one of those rescues.

Another new project in Sur's lab focuses on the neural and circuit roots of Rett motor symptoms, focusing on differences in noradrenaline expression and release in the motor cortex.

Immune insights

Sur also collaborates with Picower Institute Associate Professors Gloria Choi and Myriam Heiman and Harvard immunologist Jun Huh on a project to determine whether delivering immune system molecules to the brain could relieve social behavior abnormalities observed in multiple ASDs.

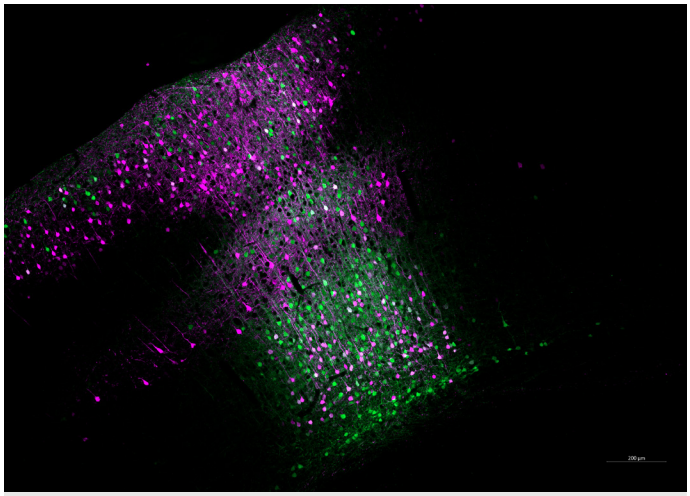
The idea's origin traces back to Choi and Huh's days in graduate school at Caltech where, based on observations that maternal infection correlated with increased autism risk, professor Paul Patterson had posited a connection. With Patterson's hypothesis on her mind, Choi came to MIT in 2013 interested in pursuing studies of how the immune system and central nervous systems interact, a young field called neuroimmunology. Patterson's hypothesis seemed like a good project to pursue in that larger context.

In a series of papers between 2016 and this past April (see page 3), Choi and Huh have made huge inroads using mice. Taken together, the studies revealed that in pregnant dams with a particular microbiome, infection can prompt immune cells to produce an excess of the immune system signaling molecule IL-17A. When the molecule reaches a particular surface region of the fetus's developing brain called S1DZ, that perturbs development leading to excessive neural activity. This abnormality, they showed, later manifests as ASD symptoms in the offspring as adults because S1DZ is involved in circuits that govern social behavior.

The IL-17 research also explained the so-called "fever effect." Some ASD patients experience social behavior improvements when they are sick. In a 2019 study, the pair discovered that mice affected by maternal infection *in utero* will produce excess IL-17A when they get an infection as adults. At this later time in life, however, the IL-17A has the effect of calming neural hyperactivity in S1DZ, leading to the improved social behavior. The newest paper shows that IL-17A promotes some S1DZ neurons to make IL-17E, which is actually what does the calming. Meanwhile, they've also discovered that a few other ASD mouse models show improved social behavior if either IL-17A or IL-17E is delivered therapeutically (for instance via a nasal spray).

"We started with one model based on an environmental factor (maternal infection) but our findings generalize to other models, including ones based on genetic causes," Choi said.

Choi and Huh hope to turn their insights from the "fever effect" into an widely applicable therapy. With Sur and Heiman, supported by a Simons Center grant, they are now investigating how IL-17A gets to the brain and whether they can safely manipulate those mechanisms to increase delivery of the molecule when its needed. Complementing that is a project, funded by the Marcus Foundation, to study the fever effect in humans. Working with colleagues at the Lurie Center for Autism at



Neurons in the S1DZ region of the mouse cortex expressed the IL17RA receptor (green), the IL-17RB receptor (magenta), or sometimes both. Those that expressed both were found to be important in IL-17 regulation of social behavior. *Image courtesy: Tomoe Ishikawa*

Massachusetts General Hospital they are recruiting autistic volunteers who do or don't experience the fever effect to provide biological samples and undergo behavioral evaluations. The hope is to rigorously document the fever effect from behavior to molecular correlates to understand more about how it works.

Network broadcasts

Many behaviors, especially cognition, are the products billions of synapses connecting millions of neurons in multiregional networks. Picower Professor Earl K. Miller is an expert in understanding how these networks operate with the speed and flexibility to enable our intellectual abilities. He's shown over numerous studies that the brain coordinates this complex neural activity with brain waves of different frequencies, almost like radio broadcasts.

As noted above, scientists hypothesize that making predictions is an ability that differs in ASDs. It may contribute to why many autistic people experience a feeling of sensory overload. Prediction enables the brain to filter out what stimuli are mundane so it can focus on what's new and salient. In a new Simons Center-funded project, Miller's lab is part of a team investigating in animals and human volunteers whether the differences in prediction seen in autism are reflected by differences in how the brain employs brainwaves to coordinate its networks. Typically, low-frequency "beta" waves would filter the activity of higher-frequency "gamma" waves that encode new sensory information. Miller's team hypothesizes that the beta waves are reduced in autistic patients. If that's true, then a potential therapeutic strategy would be to find ways to amplify beta wave activity.

"If you harness these brain rhythms you can actually treat neuropsychiatric disorders," Miller said.

Across five labs and many scales, Picower Institute researchers are bringing their expertise about how the brain works to improve understanding and treatment for ASDs.

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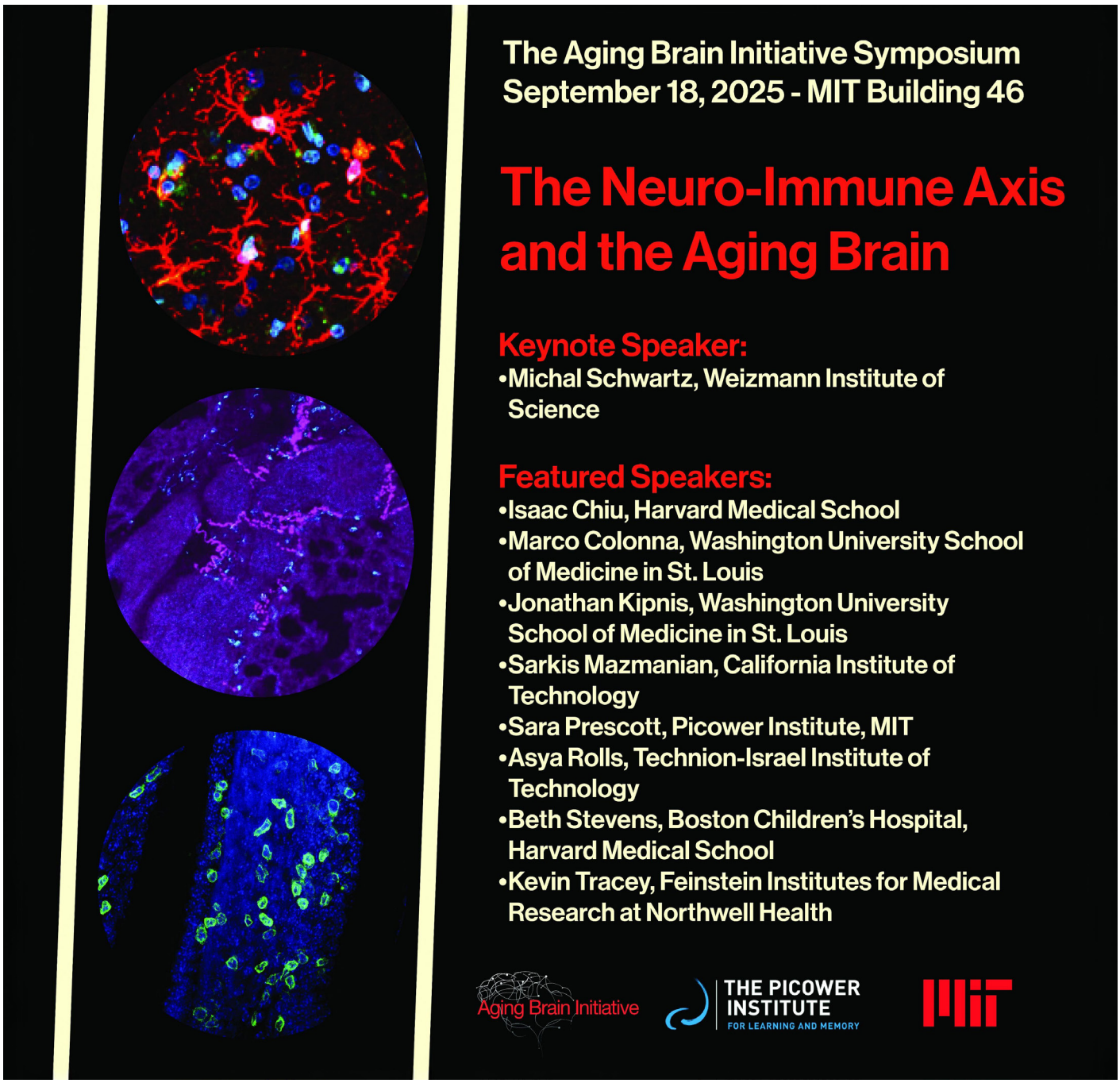

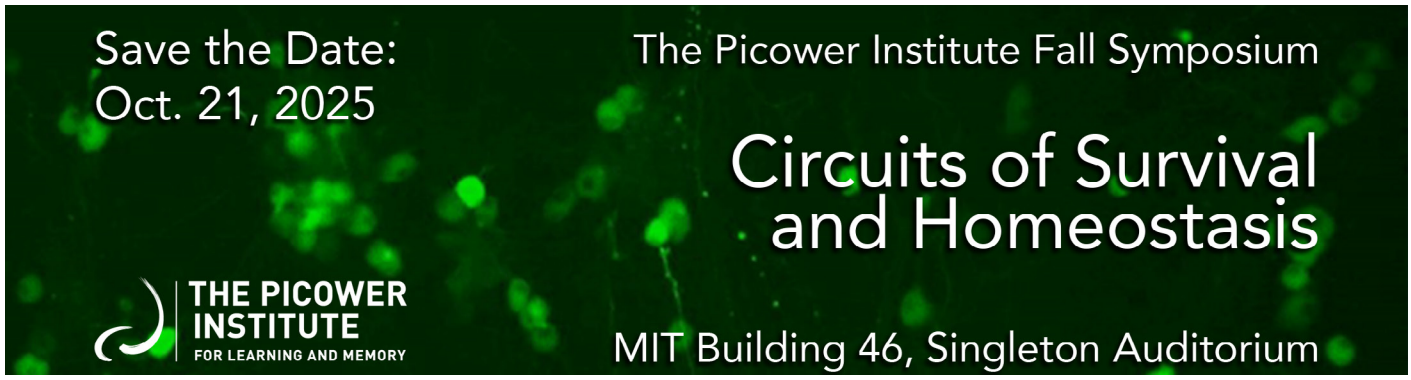

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BOTTOM ROW: **Earl Miller**, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences; **Elly Nedivi**, William R. (1964) & Linda R. Young Professor of Neuroscience, Departments of Brain and Cognitive Sciences and Biology; **Sara 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, Director, The Picower Institute for Learning and Memory; **Brady Weissbourd,** Assistant Professor of Biology; **Matthew Wilson**, Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology, Associate Director, The Picower Institute for Learning and Memory.