# Brain Simulation

**Picower Institute researchers and collaborators are inventing versatile new models of the brain to accelerate neuroscience discoveries and biomedical advances. Pg. 9**

# Neuroscience News

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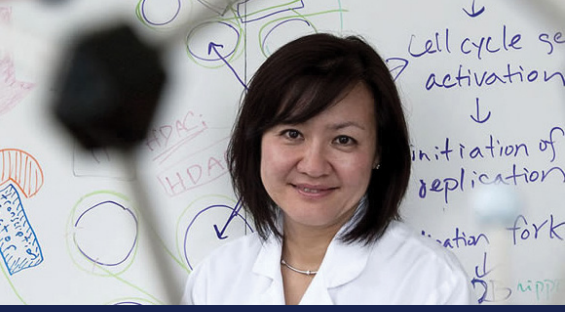
THE PICOWER INSTITUTE FOR LEARNING AND MEMORY




## DIRECTOR'S **MESSAGE**

Dear Friends,

Discovery depends on asking the right questions, but one cannot go far in science without ways of conducting the experiments to seek the answers. Neuroscience requires not only curiosity but also ingenuity.

In the next several pages you can see a wide variety of our discoveries. By necessity these each involved innovative methods.

To invent a tool for resolving the critical bundles of nerve fibers that run through the brainstem, Emery N. Brown's team harnessed A.I. (p. 6).

To learn why illness makes us want to curl up in bed, Gloria Choi's collaboration molecularly mapped the brain's receptors for immune system signals (p.2).

To investigate how neurons take on individual differences, Troy Littleton's lab sequenced the RNA in hundreds of them (p. 7).

To advance a treatment for the vision disorder amblyopia, Mark Bear's group boldly experimented with temporarily anesthetizing the retina (p.3).

To determine how a particular type of neuron influences brain development, Elly Nedivi's lab combined her own innovative imaging techniques with tissue processing advances by colleague Kwanghun Chung (p.6).

To reveal how the brain's executive control center influences other regions, Mriganka Sur's lab employed many advanced methods (p.7).

In our cover story (p. 9), we focus on two examples where collaborations between Picower neuroscientists and engineers at MIT and beyond have led to two new ways of simulating the brain. Brain simulation is an exciting emerging area because having brain models like the personalized "miBrain" human tissue culture or the "Neuroblox" computer simulation enables us to run experiments in high-volume and with great flexibility. That isn't always available with animal models and certainly not with human volunteers.

These simulations that my lab and Earl K. Miller's team have developed with collaborators therefore expand our research capabilities, complementing other methods. Indeed, we each demonstrated our respective simulations with new discoveries.

Ultimately our goal is discovery, whether it be of fundamental truths or new therapeutics (or both!). That starts with a question, but it only moves forward when we figure out–or invent–the way to ask it.

**LI-HUEI TSAI, DIRECTOR**

*The Picower Institute for Learning and Memory*

# How the brain and immune system promote staying in bed

When infection strikes, social contact often shuts down. A new study details how the immune and central nervous systems implement this sickness behavior.

It makes perfect sense that when we're battling an infection, we lose our desire to be around others. That protects them from getting sick and lets us get much needed rest. What hasn't been as clear is how this behavior change happens.

In *Cell*, Picower Institute scientists and collaborators used multiple methods to demonstrate causally that when the immune system cytokine interleukin-1 beta (IL-1β) reaches the IL-1 receptor 1 (IL-1R1) on neurons in a brain region called the dorsal raphe nucleus, that activates connections with the intermediate lateral septum to shut down social behavior.

"Our findings show that social isolation following immune challenge is self-imposed and driven by an active neural process, rather than a secondary consequence of physiological symptoms of sickness, such as lethargy," said Associate Professor and study co-senior author Gloria Choi.

Jun Huh, Harvard Medical School associate professor of immunology, is the paper's co-senior author. The lead author is Liu Yang, a research scientist in Choi's lab.

Yang and her colleagues injected 21 different cytokines into the brains of mice, one by one, to see if any triggered social withdrawal the same way that giving mice LPS (a standard way of simulating infection) did. Only IL-1β injection fully recapitulated the same social withdrawal behavior as LPS.

IL-1β affects cells when it hooks up with the receptor IL-1R1, so the team next went looking across the brain for where neurons express the receptor. The dorsal raphe nucleus (DRN) region stood out, both because it is known to modulate social behavior and because it is situated next to the cerebral aqueduct, which would give it plenty of exposure to incoming cytokines in cerebrospinal fluid. The experiments identified populations of DRN neurons that express IL-1R1.

From there, Yang and the team demonstrated that IL-1β activates those neurons, and that activating the neurons promotes social withdrawal. Moreover, they showed that inhibiting that neural activity prevented social withdrawal in mice treated with IL-1β, and they showed that shutting down the IL-1R1 in the DRN neurons also prevented social withdrawal behavior after IL-1β injection or LPS exposure.

"Our findings implicate IL-1β as a primary effector driving social withdrawal during systemic immune activation," the researchers wrote in *Cell*.

With the DRN identified as the site where neurons receiving IL-1β drove social withdrawal, the next question was what circuit they effected that behavior change through. The team traced where the neurons make their circuit projections and found several regions that have a known role in social behavior. Using optogenetics, a technology that engineers cells to become controllable with flashes of light, the scientists were able to activate the DRN neurons' connections with each downstream region. Only activating the DRN's connections with the intermediate lateral septum caused the social withdrawal behaviors seen with IL-1β injection or LPS exposure.

"Collectively, these results reveal a role for IL-1R1-expressing DRN neurons in mediating social withdrawal in response to IL-1β during systemic immune challenge," the researchers wrote.

# Study shows how **vision** can be 'rebooted' in adults with amblyopia

In amblyopia, impaired vision in one eye during development causes neural connections in the brain's visual system to shift toward supporting the other eye, leaving the amblyopic eye less capable even after the original impairment is corrected. Current interventions are only effective during infancy and early childhood while the neural connections are still being formed. But a new study in mice by neuroscientists in The Picower Institute shows that if the retina of the amblyopic eye is anesthetized just for a couple of days, the brain's visual response to the eye can be restored even in adulthood.

The findings in *Cell Reports* may improve the clinical potential of the idea of temporarily anesthetizing a retina to restore the strength of the amblyopic eye's neural connections. In 2021, the lab of Picower Professor Mark Bear and collaborators showed that anesthetizing the non-amblyopic eye could improve vision in the amblyopic one—an approach analogous in that way to the treatment used in childhood of patching the unimpaired eye. Those 2021 findings have now been replicated in adults of multiple species. But the new evidence on how inactivation works suggests that the proposed treatment also could be effective when applied directly to the amblyopic eye, Bear said, though a key next step will be to again show that it works in additional species and, ultimately, people.

"If it does, it's a pretty substantial step forward because it would be reassuring to know that vision in the good eye would not have to be interrupted by treatment," Bear said. "The amblyopic eye, which is not doing much, could be inactivated and 'brought back to life' instead. Still, I think that especially with any invasive treatment, it's extremely important to confirm the results in higher species with visual systems closer to our own."

Madison Echavarri-Leet, a former graduate student, is the lead author.

Bear's lab has been studying the science underlying amblyopia for decades. The research has produced ideas about how to address amblyopia in adulthood. In a 2016 study with collaborators at Dalhousie University they showed that temporarily anesthetizing both retinas could restore vision loss in amblyopia. Then five years later, they published the study showing that anesthetizing just the non-amblyopic eye produced visual recovery for the amblyopic eye.

Throughout that time, the lab weighed multiple hypotheses to explain how retinal inactivation works its "magic." Lingering in the lab's results, Bear said, was an unexplored finding in the lateral geniculate nucleus (LGN) that relays information from the eyes to the visual cortex, where vision is processed. Back in 2008 they had found that blocking inputs from a retina to neurons in the LGN caused those neurons to fire synchronous "bursts" of electrical signals to downstream neurons in the visual cortex.

The new study tested whether those bursts might have a role in the potential amblyopia treatments the lab was reporting. To get started, Leet and Bear's team used a single injection of tetrodotoxin (TTX) to anesthetize retinas in the lab animals. They found that the bursting occurred not only in LGN neurons that received input from the anesthetized eye, but also in LGN neurons that received input from the unaffected eye.

From there they showed that the bursting response depended on a particular "T-type" channel for calcium in the LGN neurons. This was important because knowing this gave the scientists a way to turn it off. Once they gained that ability, then they could test whether doing so prevented TTX from having a therapeutic effect in mice with amblyopia.

Sure enough, when the researchers genetically knocked out the channels and disrupted the bursting, they found that anesthetizing the non-amblyopic eye could no longer help amblyopic mice. That showed the bursting is necessary for the treatment to work.

Given their finding that bursting occurs when either retina is anesthetized, the scientists hypothesized it might be enough to just do it in the amblyopic eye. To test this, they ran an experiment in which some mice modeling amblyopia received TTX in their amblyopic eye and some did not. The injection took the retina offline for two days. After a week the scientists then measured activity in neurons in the visual cortex to calculate a ratio of input from each eye. They found that the ratio was much more even in mice that received the treatment vs. those left untreated, indicating that after the amblyopic eye was anesthetized, its input in the brain rose to be at parity with input from the non-amblyopic one.

# Brain **waves'** analog organization of cortex enables cognition and consciousness

Over 30 years in his MIT lab, Picower Professor Earl K. Miller has studied how the brain's cortex produces thought. In an invited lecture at the Society for Neuroscience annual meeting, he proposed to an audience of thousands that cognition and consciousness emerge from the dynamic organization of the cortex produced by traveling brain waves performing analog computations.

Analog computing is an old idea that embraces how information in the real world is continuous, not chopped up into digital binary bits. Just two waves colliding with each other can smoothly represent any value from the negative to the positive sum of their amplitudes simply based on their phase. Miller says it's no coincidence that the brain, where the coordinated electrical activity of millions of neurons produces large-scale oscillations across a broad range of frequencies all the time, evolved to exploit the information-rich, fast-propagating, and reliable efficiency that its waves provide.


Earl K. Miller delivers his talk at the Society for Neuroscience Annual Meeting Nov. 15

"What is needed for top-down executive control of the brain?" asked Miller. "I propose it requires large-scale, dynamic neural self organization. How can the activity of millions and millions of neurons be organized on the fly? Brain waves are organization."

The nature of consciousness is a hotly debated topic, but many biologically based theories agree that a unified awareness of thought and experience requires a cortex unified by information exchange. Miller says what his evidence adds to such ideas is that brain waves not only unify the cortex, but also organize it with analog computation to control and accomplish information processing.

In 2001, Miller co-authored a seminal review paper arguing that the prefrontal cortex implements executive control of the brain by actively maintaining goal-directed activity patterns that bias the functions of other regions. He and colleagues also showed that many neurons in the prefrontal cortex are not dedicated to specific tasks, like gears in a machine, but instead can participate in multiple networks at once.

But what organizes these neural networks to implement widespread, goal-directed function? The answer began to emerge in 2007, when Miller's lab published the first in a long series of papers—continuing through the present day—that show how patterns of neural oscillations can sculpt information flow across the cortex. "Top-down" goal-directed signals (the brain's internal sense of the rules), are encoded in relatively slow alpha and beta frequency waves (15-35 Hz) while incoming sensory information is encoded in higher frequency gamma waves (35-60Hz). Subsequent studies have shown that in cognitive functions, the beta waves constrain the power of the gamma waves, essentially imposing the brain's goals on information processing. This regime enables volitional control of thought: When you want to retrieve information committed to working memory (like today's specials at a restaurant), your cortex can relax beta power to let gamma fetch that for you.

Miller's theory of Spatial Computing (see p. 5) explains how the brain recruit neurons into functional networks: by applying waves within physical patches in the cortex. Beta waves essentially act like stencils that constrain gamma activity in those patches. When goals and rules (represented by beta) dictate that information represented by the neurons in a patch are needed, gamma wave power can rise to enable retrieval and processing of that information.

To Miller, "consciousness is the tip of the iceberg of cognition." Brain waves and their analog computations do a lot of cognitive work without your explicit intervention, but they also enable volitional control. For instance, you don't always consciously direct your brain to keep track of potential changes in your environment (e.g. a sudden peal of thunder), but it can surface those changes when it spots them to enable you to consciously think about what to do (going back inside to get a raincoat).

"Consciousness may be a natural outcome of analog computation," Miller says. "Consciousness is good for flexibility and planning and the kind of big picture stuff that needs a unified representation. When the analog computations create wave patterns that are large enough to unify cortex, you get consciousness."

In numerous recent studies, Miller and colleagues have connected consciousness to brain wave dynamics by looking at how general anesthesia affects them. They've shown that anesthesia disrupts the power of waves in different frequencies, knocking them out of the normal beta-gamma balance needed to organize cognition. They have shown that anesthesia disrupts propagation of waves linking sensory and higher order regions of the cortex that provides unification and organization. They have shown that anesthesia alters the travels of traveling waves. And in a study last year, the lab also showed that distinct anesthetic drugs push brain waves out of phase with each other, which would disrupt their ability to engage in analog computations.

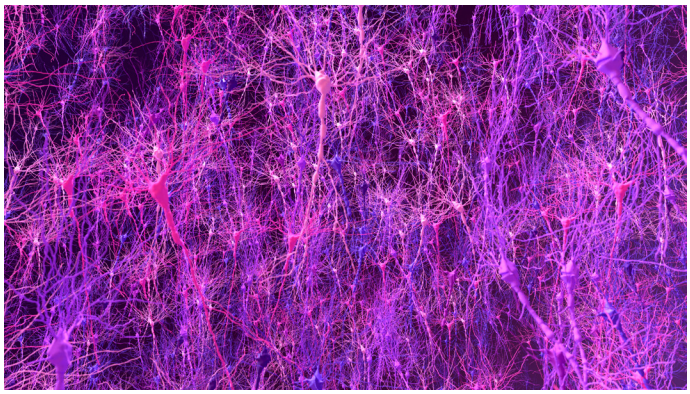
# Biology-based brain model **learns,** enables new discovery

A new computational model of the brain based closely on its biology and physiology not only learned a simple visual category learning task exactly as well as lab animals, but even enabled the discovery of counterintuitive activity by a group of neurons that researchers working with animals to perform the same task had not noticed in their data before, said a team of scientists at Dartmouth College, MIT, and SUNY Stony Brook (*also see cover story*).

Notably, the model described in *Nature Communications* produced these achievements without ever being trained on any data from animal experiments. Instead, it was built from scratch to faithfully represent how neurons connect into circuits and then communicate electrically and chemically across broader brain regions to produce cognition and behavior. Then, when the research team asked the model to perform the same task that they had previously performed with the animals, it produced highly similar neural activity and behavioral results, acquiring the skill with almost exactly the same erratic progress.

A goal in making the model, and newer iterations developed since the paper was written, is not only to offer insight into how the brain works, but also how it might work differently in disease and what interventions could correct those aberrations, said co-author Earl K. Miller, Picower Professor in The Picower Institute.

The model is built from "primitives," or small circuits of a few neurons each that connect based on electrical and chemical principles of real cells, to perform fundamental computational functions. At a larger



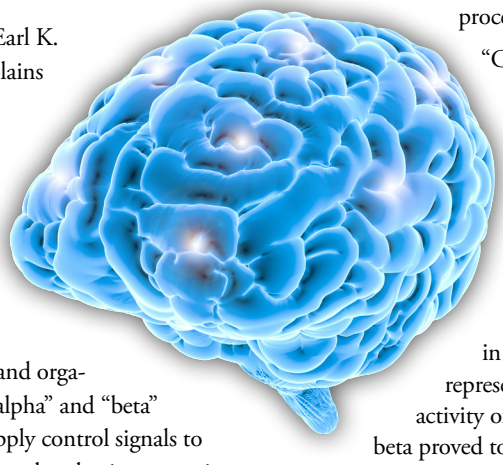
scale, the model encompasses four brain regions needed for basic learning and memory tasks: a cortex, a brainstem, a striatum and a "tonically active neuron" (TAN) structure.

As the model demonstrated learning much like real animals, it also presented the researchers with a group of neurons—about 20 percent—whose activity appeared highly predictive of error. When these "incongruent" neurons influenced circuits, the model would make the wrong category judgement. At first, the team figured it was a quirk of the model. But then they looked at the real-brain data Miller's lab accumulated when animals performed the same task and found neurons doing that same thing. Previously those cells and their activity hadn't been identified.

# Brain uses space to organize **thought**

How does well-controlled and yet highly nimble cognition emerge from the brain's anatomy of billions of neurons and circuits? A new study by Picower Institute researchers provides new evidence that the answer might be a theory called "Spatial Computing."

First proposed in 2023 by Picower Professor Earl K. Miller and colleagues, Spatial Computing explains how neurons in the prefrontal cortex can be organized on the fly into a functional group capable of carrying out the information processing required by a cognitive task. Moreover, it allows for neurons to join multiple groups, as years of experiments have shown that many prefrontal neurons can indeed participate in multiple tasks at once. The basic idea is that the brain recruits and organizes ad hoc task forces of neurons by using "alpha" and "beta" frequency brain waves (about 10-30 Hz) to apply control signals to physical patches of the prefrontal cortex. Rather than having to rewire themselves into new physical circuits every time a new task must be done, the neurons in the patch instead process information by following the patterns of excitation and inhibition imposed by the waves.



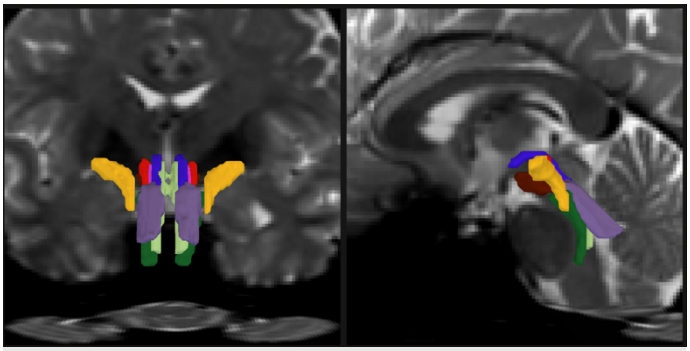
Think of the alpha and beta frequency waves as stencils that shape when and where groups of neurons can take in or express information from the senses, Miller said. In that way, the waves represent the rules of the task and can organize how the neurons electrically "spike" to process the information content needed for the task.

"Cognition is all about large-scale neural self-organization," said Miller, senior author of the paper in *Current Biology*.

A theory is just an idea. In the study, lead author Zhen Chen and co-authors put Spatial Computing to the test by examining whether the predictions it makes about neural activity and brain wave patterns were evident in measurements made in animals as they engaged in cognitive tasks. Indeed, alpha and beta waves represented task controls and rules, while the spiking activity of neurons represented sensory inputs. Alpha and beta proved to be spatially organized. When and where they were strong, the sensory information represented by spiking would be suppressed but where and when it was weak, spiking would increase. Finally, trial by trial alpha/beta power and timing correlated with the animals' performance.

# AI enables tracking of **brainstem** nerve bundles

The signals that drive many of the brain and body's most essential functions—consciousness, sleep, breathing, heart rate and motion—course through bundles of "white matter" fibers in the brainstem, but imaging systems so far have been unable to finely resolve these crucial neural cables. In a new study, a team of MIT, Harvard, and Massachusetts General Hospital researchers unveil AI-powered software capable of automatically segmenting eight distinct bundles in any diffusion MRI sequence.



Two cross-section views of a human brain show individual segmented and color-coded nerve bundles in the brainstem.

The research team led by MIT graduate student Mark Olchanyi reports in the *Proceedings of the National Academy Sciences* that their BrainStem Bundle Tool (BSBT) revealed distinct patterns of structural changes in patients with Parkinson's disease, multiple sclerosis, and traumatic brain injury and shed light on Alzheimer's disease as well.

Moreover, the study shows, BSBT retrospectively enabled tracking of bundle healing in a coma patient that reflected the patient's 7-month road to recovery.

"The brainstem is one of the body's most important control centers," said senior author and Olchanyi's thesis supervisor Emery N. Brown, Picower Institute investigator and Edward Hood Taplin Professor at MIT. "Mark's algorithms are a significant contribution to imaging research and to our ability to understand regulation of fundamental physiology. By enhancing our capacity to image the brainstem, he offers us new access to vital physiological functions such as control of the respiratory and cardiovascular systems, temperature regulation, how we stay awake during the day and how we sleep at night."

Diffusion MRI helps trace the long branches, or "axons," that neurons extend to communicate with each other. Axons are typically clad in a sheath of fat called myelin and water diffuses along the axons within the myelin. Diffusion MRI can highlight this very directed displacement of water. BSBT works by tracing fiber bundles that plunge into the brainstem from neighboring areas higher in the brain such as the thalamus and the cerebellum to produce a "probabilistic fiber map." An artificial intelligence module called a "convolutional neural network" then combines the map with several channels of imaging information from within the brainstem to distinguish eight individual bundles.

The researchers used BSBT to track scores of cases of neurodegeneration or injury, demonstrating that the tool might provide useful biomarkers.

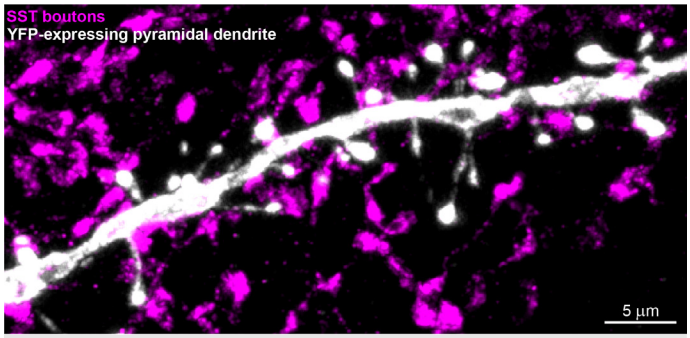
# Unique neuron class may set up brain development

The way the brain develops can shape us throughout our lives, so neuroscientists are intensely curious about how it happens. A new study in mice by Picower Institute researchers reveals that an important class of neurons follows a set of rules that while surprising, might just create the right conditions for circuit optimization during development.

During early brain development, multiple types of neurons emerge in the visual cortex (where the brain processes vision and where this study focused). Many are "excitatory," driving the activity of brain circuits, and others are "inhibitory," meaning they control that activity. Just like a car needs not only an engine and a gas pedal, but also a steering wheel and brakes, a healthy balance between excitation and inhibition is required for proper brain function. During a "critical period" of development, soon after the eyes first open, excitatory and inhibitory neurons forge and edit millions of connections, or synapses, to adapt nascent circuits to the incoming flood of visual experience. Over many days, in other words, the brain optimizes its attunement to the world.

In the new study in *The Journal of Neuroscience*, a team led by MIT research scientist Josiah Boivin and Professor Elly Nedivi visually tracked somatostatin (SST)-expressing inhibitory neurons forging synapses with excitatory cells along their sprawling dendrite branches, illustrating the action before, during and after the critical period with unprecedented resolution. Several of the rules the SST cells appeared to follow were unexpected—for instance, unlike other cell types their activity did not depend on visual input—but now that the scientists know these neurons' unique trajectory, they have a new idea about how it may enable sensory activity to influence development: SST cells might help usher in the critical period by establishing the baseline level of inhibition needed to ensure that only certain types of sensory input will trigger circuit refinement.

"Why would you need part of the circuit that's not really sensitive to experience? It could be that it's setting things up for the experience dependent components to do their thing," said Nedivi, William R. and Linda R. Young Professor.




Researchers used eMAP (developed by Professor Kwanghun Chung) to zoom in on an excitatory dendrite (white) in the visual cortex and see where SST Boutons (magenta) connected via synapses.

# Prefrontal cortex influences how other regions function

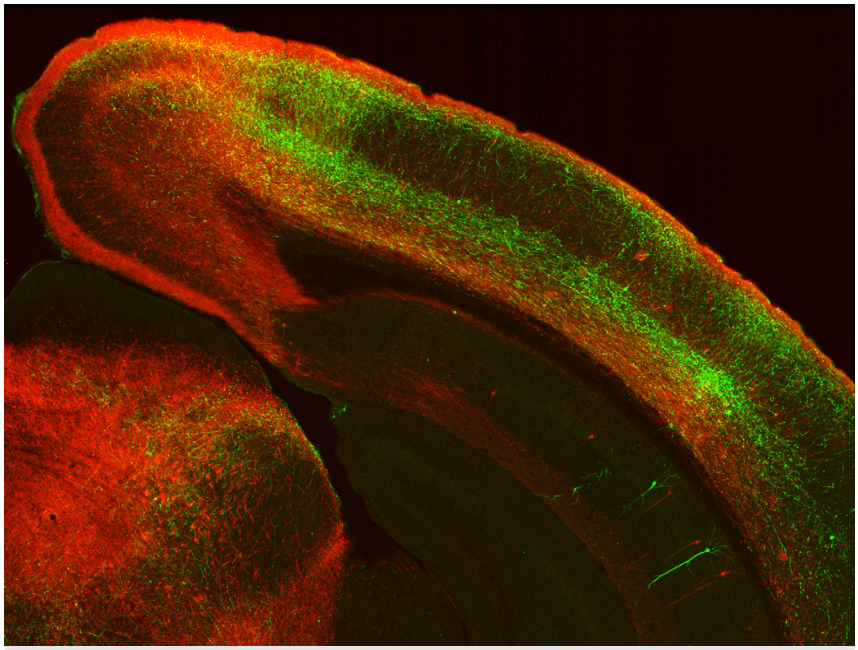
Vision shapes behavior and, a new study in *Neuron* by MIT neuroscientists finds, behavior and internal states shape vision. The research finds in mice that the brain's executive control center, the prefrontal cortex, sends tailored messages via specific circuits to regions governing vision and motion to ensure that their work is shaped by contexts such as the mouse's level of arousal and whether they are on the move.

"That's the major conclusion of this paper: There are targeted projections for targeted impact," said senior author Mriganka Sur, Paul and Lilah Newton Professor in The Picower Institute.

Neuroscientists have long suggested that the prefrontal cortex biases the work of regions further back in the cortex. Tracing of anatomical circuits supports this idea. But in the new study, lead author and Sur Lab postdoc Sofie Ährlund-Richter sought to determine whether the PFC is broadcasting a generic signal or customizes the information it conveys for different downstream regions. She also wanted to take a fresh look at which neurons the PFC talks to, and what impact the information has on how those regions function.

Ährlund-Richter and Sur's team uncovered several new revelations. One was that the two prefrontal areas they focused on, the orbitofrontal cortex (ORB) and the anterior cingulate area (ACA), selectively convey information about arousal and motion to the two downstream regions they studied, the primary visual cortex (VISp) and the primary motor cortex (MOp), to achieve distinct ends. For instance, the more aroused a mouse was the more ACA prompted VISp to sharpen the focus of visual information it represented, but ORB only chimed in if arousal was very high and then its input seemed to reduce the sharpness of visual encoding. Ährlund-Richter speculates that as arousal increases, ACA may help the visual cortex focus on resolving what might be salient in what it's seeing, while ORB might be suppressing focus on unimportant distractors.

"These two PFC subregions are kind of balancing each other," Ährlund-Richter said. "While one will enhance stimuli that might be more uncertain or more difficult to detect, the other one kind of dampens strong stimuli that might be irrelevant."



An image from the research shows where neurons from the ACA (red) and ORB (green) regions of the prefrontal cortex innervate the visual cortex.

# RNA editing study shows how neurons diversify

All starting from the same DNA, neurons ultimately take on individual characteristics in the brain and body. Differences in which genes they transcribe into RNA help determine which type of neuron they become, and from there, a new MIT study shows, individual cells edit a selection of sites in those RNA transcripts, each at their own widely varying rates.

The new study surveyed the whole landscape of RNA editing in more than 200 individual cells commonly used as models of fundamental neural biology: tonic and phasic motor neurons of the fruit fly. One of the main findings is that most sites were edited at rates between the "all or nothing" extremes many scientists have assumed based on more limited studies in mammals, said senior author Troy Littleton, Menicon Professor in The Picower Institute. The resulting dataset and analyses in *eLife* set the table for discoveries about how RNA editing affects neural function and what enzymes implement those edits.

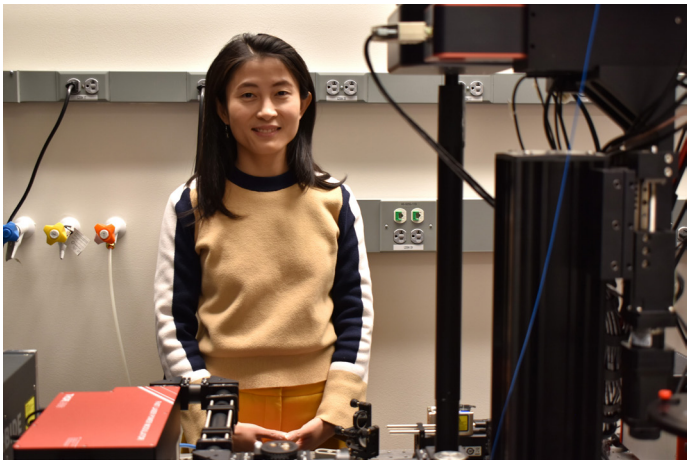
"We have this 'alphabet' now for RNA editing in these neurons," Littleton said. "We know which genes are edited in these neurons so we can go in and begin to ask questions as to what is that editing doing to the neuron at the most interesting targets."

Andres Crane, who earned his PhD in Littleton's lab based on this work, is the study's lead author.

From a genome of about 15,000 genes, Littleton and Crane's team found, the neurons made hundreds of edits in transcripts from hundreds of genes. For example, the team documented "canonical" edits of 316 sites in 210 genes. Canonical means that the edits were made by the well-studied enzyme ADAR, which is also found in mammals including humans. Of the 316 edits, 175 occurred in regions that encode the contents of proteins. Analysis indeed suggested 60 are likely to significantly alter amino acids. But they also found 141 more editing sites in areas that don't code for proteins but instead affect their production, which means they could affect protein levels, rather than their contents.

The team also found many "non-canonical" edits. That's important, Littleton said, because that information could aid in discovering more enzymes involved in RNA editing, potentially across species. That, in turn, could expand the possibilities for future genetic therapies.

# Sloan Fellowship will help **Fan** advance technology to study how brain circuits change amid learning



In her Picower Institute lab, Assistant Professor Linlin Fan seeks to discern the rules and processes by which the brain encodes and stores memories during learning. To do that, she has helped to pioneer "all-optical physiology," a set of technologies that allows neuroscientists to use light to precisely manipulate the activity of neurons in live animals and read out the effects that has on the neurons they connect with in circuits. With a new fellowship from the Alfred P. Sloan Foundation, she plans to advance the technique to enable investigation of larger volumes of cells deeper in the brain.

Neuroscientists theorize that the brain encodes and stores memories by making changes to connections, or "synapses" among neurons to form new circuits. Directly investigating and testing the process in action to understand the rules that govern it has proven tricky—some older methods are too imprecise, while others are too slow or insensitive.

In recent years, however, Fan and others have demonstrated that by combining multiple technologies, they can genetically target specific neurons in live animals to take control of their electrical activity ("optogenetics"), and engineer other neurons that those cells connect with to optically report even very subtle, quick changes in their resulting electrical responses ("genetically engineered voltage indicators"). Key to these advances has been cleverly designing microscope systems that can direct multiple light paths into a deep brain structure called the hippocampus, a major center for learning and memory, and also detect the multiple optical signals coming out, all without interference.

Still, all-optical techniques have only been able to address a few neurons at a time. Now with the $75,000, two-year support of the Sloan Fellowship, Fan said she plans to upgrade all-optical physiology to be able to engage a larger volume within the hippocampus, thereby broadening and deepening the technology's reach. The work centers on devising a way to integrate "two-photon" microscopy, which enables light to penetrate deeper into tissue.

"Having this more advanced technique will allow us to see more and to see deeper inside this structure," said Fan, a faculty member in MIT's Brain and Cognitive Sciences Department and one of eight MIT professors to earn a Sloan Fellowship this year.

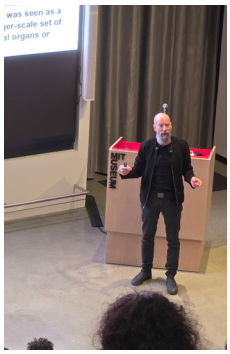
"The Sloan Research Fellows are among the most promising early-career researchers in the U.S. and Canada, already driving meaningful progress in their respective disciplines," said Stacie Bloom, president and CEO of the Sloan Foundation.

In all, the foundation awarded fellowships to 126 researchers from among more than 1,000 nominees. Fan said she is honored to have been chosen.

"I'm very grateful to the foundation for their support of our work," Fan said. "It's really a great privilege to be selected as a fellow among other great scientists. Having foundational support for science is more important than ever."

# Night at the museum

About 500 people packed the "After Dark" event "Memory Lab" co-produced by the MIT Museum and The Picower Institute Feb. 12. Professors Matt Wilson and Earl Miller gave talks. Demos included one by postdoc Takato Honda. The band Clever Hans, including Earl and Associate Professor Steve Flavell (guitars), capped the amazing evening.



# Brain Simulation

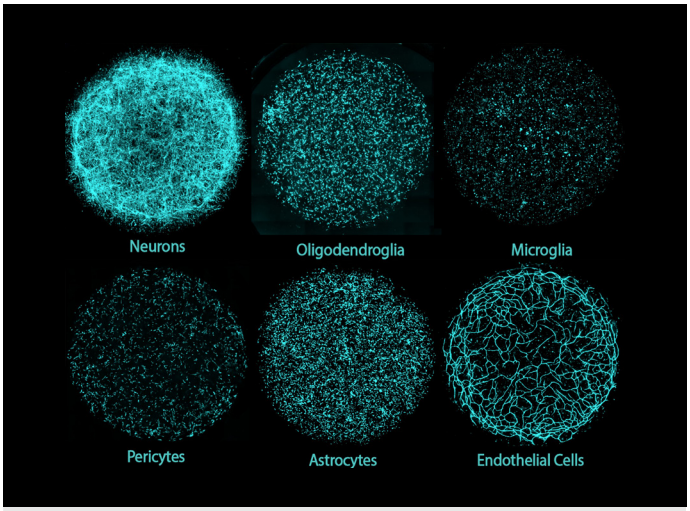
*Picower Institute researchers and collaborators are inventing versatile new models of the brain to accelerate neuroscience discoveries and biomedical advances.*

When the real thing—in this case, the human brain—is rightfully out of the reach of experimental manipulation, what's the next best thing for understanding how the brain works in health, falters in disease, and could be rescued with treatment? The longtime answer has been animal models, and often that's still true. But pioneering neuroscientists and engineers are advancing another way: simulation.

Among this vanguard are Picower Professors Li-Huei Tsai and Earl K. Miller, who have each forged collaborations to produce novel simulations of the brain. Each has recently published papers about these inventions, though their teams' ongoing work means they've already surpassed those milestones and developed the technologies further.

In Tsai's case, the innovation is the "miBrain," the first 3D human brain tissue culture to include all six major brain cell types. Demonstrating that the unprecedentedly diverse mini-tissue is an advanced platform for discovery, Tsai and colleagues used it to produce a new revelation about how cellular interactions drive Alzheimer's disease. In Miller's case, the mental mimic is a biologically-based computational model of brain circuitry and dynamics called "Neuroblox." His team showed it can replicate learning behavior and revealed neural activity in its simulated circuits that had gone unnoticed in real brain data (*also see p. 5*).

Each simulation enables new paradigms of experimental manipulations to yield fundamental discoveries. They also provide advanced high-volume platforms for testing interventions and treatments to improve brain health.




miBrains fully integrate all six major brain cell types, though they are each highlighted separately here.

"The idea is to make a platform for biomimetic modeling of the brain so you can do things like drug development and drug testing earlier in the process, providing a more efficient way of developing neural therapies," said Miller, one of the six founders of the Neuroblox startup company led by CEO Lilianne R. Mujica-Parodi.

Like Neuroblox, miBrain offers new research options, Tsai said.

"The miBrain can develop human-specific pathological features without ectopically overexpressing a particular human disease gene, as one must do with animal models of human diseases," Tsai said. "Also, it is possible to create personalized miBrains using skin cells donated by patients. Finally, the miBrain culture is very amenable to drug treatment. Therefore, the miBrain can be used as a parallel system to animal models."

## A culture of ingenuity

For years, Tsai's lab has been using 3D human cell cultures (as have Picower colleagues Kwanghun Chung and Mriganka Sur). But keenly aware of how complex the brain, and the Alzheimer's pathology that afflicts it, can be, Tsai sought to integrate all six major cell types: neurons, microglia, oligodendrocytes, astrocytes, pericytes and endothelial cells.

The work began in 2019 with a grant that Tsai and former postdoc Joel Blanchard earned from the National Institutes of Health. They teamed up with the chemical engineering and bioengineering lab of MIT Institute Professor Robert Langer. In an October 2025 paper in the *Proceedings of the National Academy of Sciences*, led by former postdocs Alice Stanton and Adele Bubnys, they published their landmark result: the multicellular integrated brain, or miBrain.

All cells in a miBrain derive from skin cells donated by a volunteer. Those cells are converted back into stem cells that are then transformed into the different brain cell types. Then they are combined into the full culture within an ingenious hydrogel. As such, each miBrain is a personalized model brain that carries the genome of the donor and self-assembles into functioning units, including blood vessels, immune defenses, myelinated axons, and neural circuits.

Meanwhile, the lab can grow many copies of someone's miBrain and alter any of the genes in the cells. They can also expose the miBrains to various drugs or other agents to test their effects, making them a scalable platform for personalized treatment screening.

In the *PNAS* paper, the team used miBrain to study how the APOE4 variant of the APOE gene, the biggest genetic risk factor for Alzheimer's, produces pathology such tau proteins. The role of astrocyte cells is an open question that couldn't be fully resolved just by looking at post-mortem brains or by working with a culture of astrocytes alone.

*(Continued on next page)*

Indeed, when the team cultured just APOE4 astrocytes, they found that the cells did not exhibit the same pathology-promoting immune response in lab tests that they produced in miBrains where they interacted with their fellow brain cells. Yet, pathology occurred in miBrains where the astrocytes harbored APOE4 but all the other cell types harbored the benign APOE3 version. That suggested that APOE4 compels astrocytes to promote pathology, but only in conjunction with other cells.

Data from previous studies hinted that the APOE4 astrocytes' partners in pathology might be microglia cells, so the researchers left microglia out of some miBrains. In those cases, APOE4 astrocytes did not promote pathology. And when they exposed microglia-less miBrains to doses of media from a microglia-astrocyte co-culture, they saw tau increase, but not when they seeded such miBrains with media from just microglia or astrocyte cultures alone. The modularity of miBrains allowed them to show that APOE4 astrocytes depend on interaction with microglia to promote Alzheimer's pathology.

The team has extended miBrains even further. In a preprint, the team describes clever modifications that have enabled the cultures to grow circulatory networks. By hooking them up to microfluidic systems, the scientists can perfuse the circulatory system to test therapeutic agents, including how they might fare at the formidable "blood-brain barrier" (BBB) that strictly filters what goes into or out of the brain from its blood vessels.

"The perfusable BBB allows us to introduce protein factors, peptides, chemicals and drugs into the miBrain," Tsai said. "It also permits the potential evaluation of pharmacokinetics and pharmacodynamics of drugs such as how efficiently they can cross the BBB."

## Brainy blocks

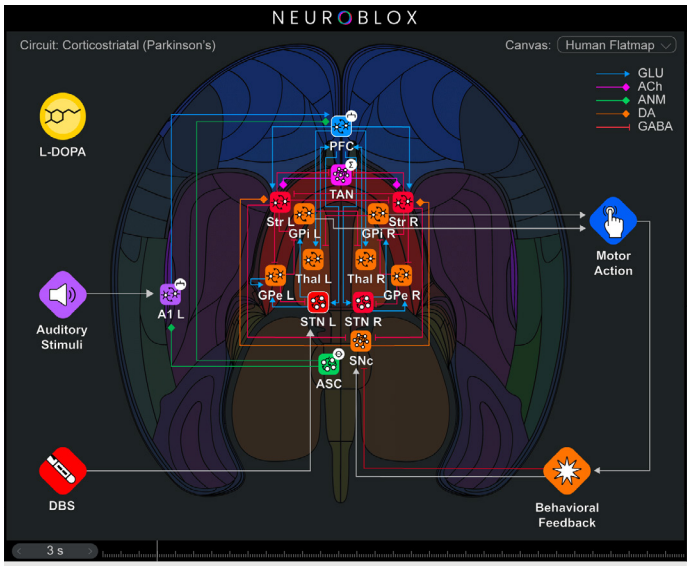
Neuroblox, too, is a fusion of neuroscience and engineering. About five years ago, Mujica-Parodi realized that neuroscience studies and therapies could be accelerated if the field had the computer simulation tools that benefit computer chip or aerospace designers. Computational models free experimenters from logistical constraints of working with animal models, so they can explore many more hypotheses at the same time.

"What we'd like to do in principle is to look at the entire set of candidate hypotheses at once, and then let the data tell us what hypotheses are compatible and not compatible with the data," she said. "It's a philosophical change in terms of how we can think about science that is only made possible because of the technological innovation."

As she built on the idea, the SUNY Stony Brook Biomedical Engineering Professor, who also holds an affiliation with The Picower Institute, assembled a "dream team" of scientists and engineers including Miller, MIT Math Professor Alan Edelman, MIT Research Affiliate Chris Rauckaukas, Stony Brook Associate Professor Helmut Strey, and Dartmouth College Professor Rick Granger. Meanwhile, to launch the effort, Mujica-Parodi received funding from philanthropists David Baszucki and Jan Ellison Baszucki.

Neuroblox owes its name, in part, to how it's built. Like an integrated circuit, it integrates fundamental computational components, also called "primitives" or "blox." Unlike a computer chip, Neuroblox is biomimetic, meaning that the blox model fundamental processing units made up of spiking neurons, experimentally derived from neuroanatomical and neurophysiological data. These primitives are the elements from which larger-scale circuits are composed, which in turn are the elements from which even larger-scale circuits are composed.

This modular, nested approach—validated against experimental brain data at every scale—extends all the way up to whole-brain computation, Mujica-Parodi said. The virtual neurons in each primitive can respond to electrical or molecular inputs, such as external sensory stimuli, signals from fellow neurons, or neuromodulators such as serotonin, metabolites, or drugs.




**Detail from a Neuroblox screenshot indicates the software's versatility**

The architecture enables the model to connect cellular and molecular activity all the way to cognition and behavior. For instance, in *Nature Communications* in December 2025, the team published the results of a critical test: They asked Neuroblox to learn a simple visual categorization task that Miller had once asked lab animals to learn. The model did so with almost exactly the same erratic progress that the animals exhibited. Underlying neural activity associated with this learning also closely resembled that of the animals. In fact, the model replicated and therefore revealed something that had remained hidden in the original lab animal data. Some cells, even as learning progresses, continue to inject error. Why? Miller speculates they might give the brain the flexibility to discover a new path forward if the rules of the task ever change.

While the study demonstrated sensory and neuromodulatory input, advances since then have enabled Neuroblox to accommodate more, Mujica-Parodi said. This has enabled the company to model anesthesia, deep brain stimulation, and even questions related to interactions between the central nervous system and other physiological systems, such as how dietary ketosis and diabetic insulin resistance affect the brain.

The model's versatility makes it ideal for accelerating the discovery of therapeutics, Mujica-Parodi and Miller said, because it can reduce the guesswork that holds back many drug studies. For instance, while scientists have become good at crafting molecules to bind to target receptors on neurons, it has been slow going to figure out what will happen in brain circuits or to behavior once the binding occurs. By enabling rapid, scalable computational testing of hypotheses, Neuroblox can help answer such questions to improve drug trials, Mujica-Parodi said.

Many methods move neuroscience forward. New simulations, both on the lab benchtop and the computer desktop, promise to move it forward faster.

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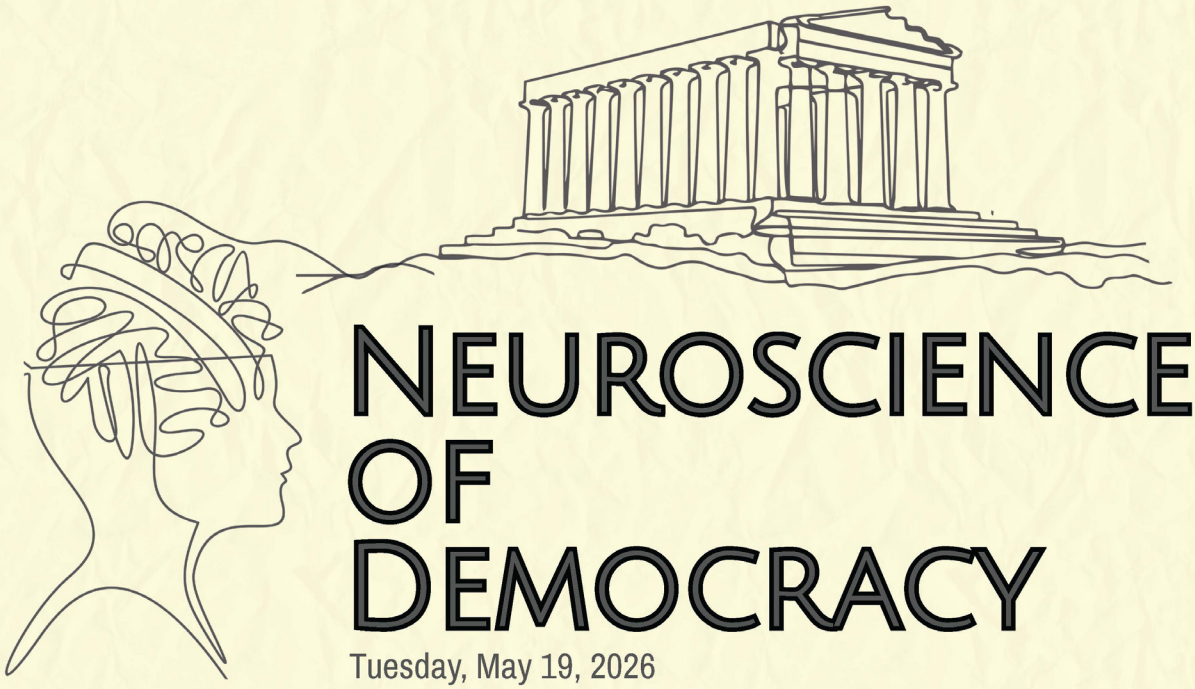

# NEUROSCIENCE OF DEMOCRACY

Tuesday, May 19, 2026
MIT Building 46 - Cambridge, MA

Keynotes by

**Stacey Abrams**, Author, Entrepreneur, and Voting Rights Activist

**Alicia Garza**, Freedom Together Foundation

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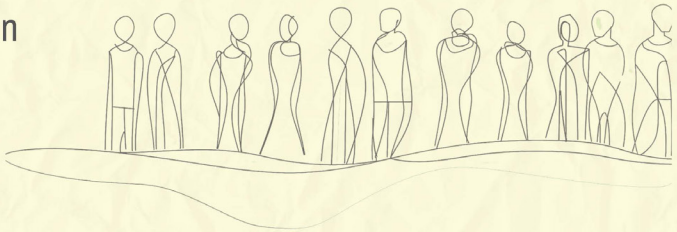
**Adam Berinsky**, MIT Political Science
**Deepak Bhargava**, Freedom Together Foundation
**Emily Falk**, University of Pennsylvania
**Earl K. Miller**, MIT Picower Institute for Learning and Memory
**Rebecca Saxe**, MIT Brain and Cognitive Sciences
**Tali Sharot**, University College London
**Lily Tsai**, MIT Political Science
**Sam Wang**, Princeton University



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The Picower Institute is a community of scientists dedicated to understanding the mechanisms that drive learning and memory and related functions such as cognition, emotion, perception, 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, 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.