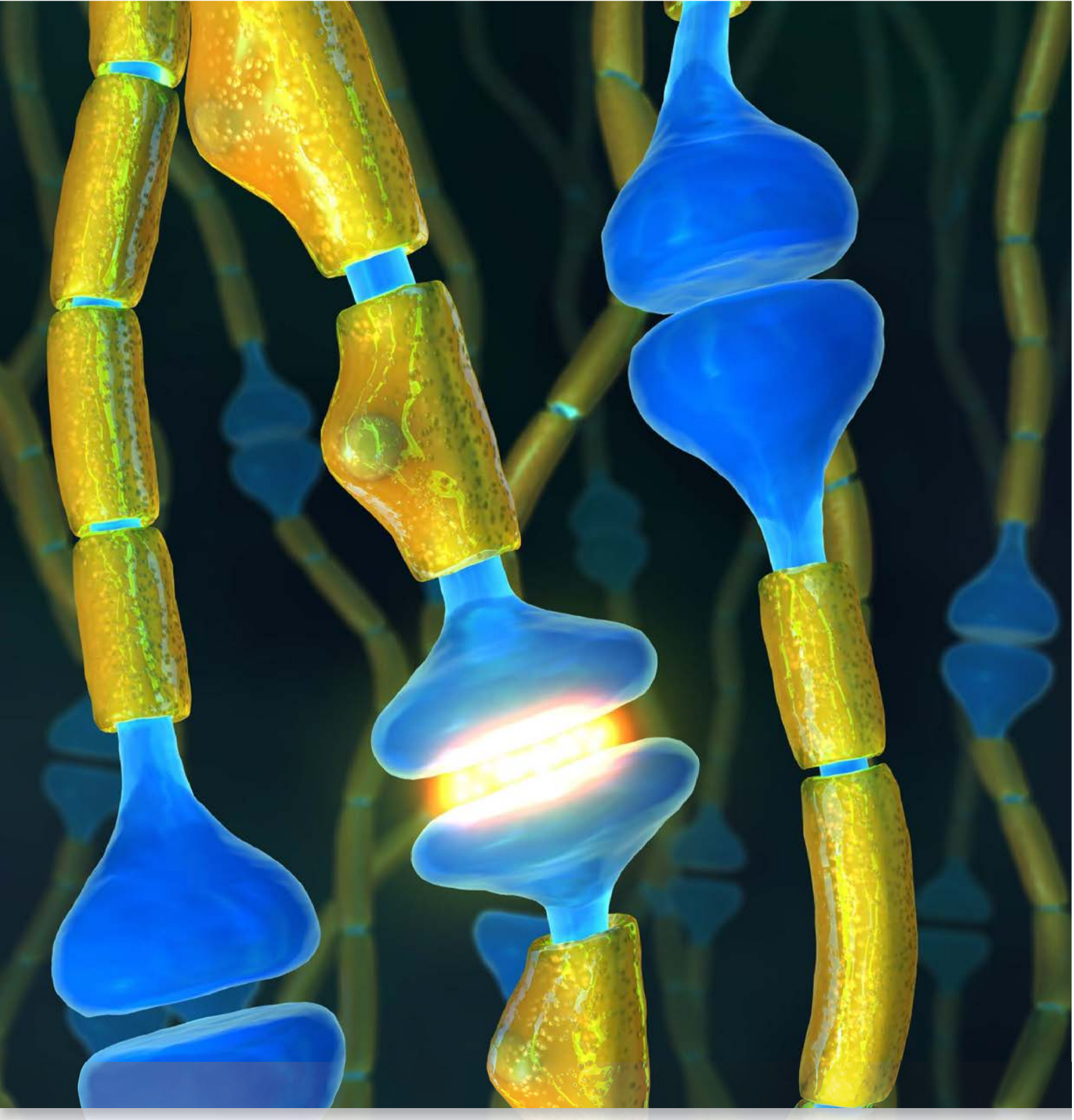
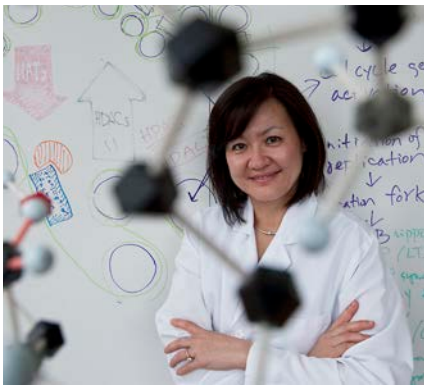


Neuroscience News

Spring 2013

THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY



Li-Huei Tsai

Director, Picower Institute for Learning and Memory

Photo / Len Rubenstein

FROM THE DIRECTOR
LI-HUEI TSAI

I am pleased to announce that for the next two years the Picower Institute Innovation Fund (PIIF) will continue to support our ability to pursue high-risk, high-reward research not typically funded by government agencies.

The PIIF has allowed Kay Tye to conduct costly optogenetic manipulation of dopamine circuits in chronically stressed animals, and to invest in cutting-edge technologies that optically probe intracellular calcium in the brains of living animals.

With the help of the PIIF, Earl Miller has been able to provide mounting evidence that the reason we can store only a few thoughts in mind simultaneously is because the brain transmits information rhythmically, in packets. He hopes to leverage these observations and non-invasive brain stimulation to expand the mind's bandwidth.

Troy Littleton has used the PIIF to explore how synaptic connections can form rapidly in a living animal during neuronal plasticity, boosting understanding of how synaptic connections are altered during memory formation, as well as how these processes go awry in neurodevelopment and neurodegenerative diseases.

Visual plasticity and psychiatric disease are not generally linked in requests for traditional funding, so the PIIF has given Mark Bear the freedom to explore the cortical circuits and synaptic plasticity mechanisms that serve long-term habituation to visual stimuli as they become familiar. This process is altered in schizophrenia, and the Bear lab may provide new insights into the pathophysiology of this disease that suggest new treatment approaches. Mark says the PIIF gave him and his colleagues the unusual opportunity to follow their curiosity and see where it leads them.

We are grateful for The JPB Foundation's continued recognition that innovative research and meaningful collaborations among scientists constitute the most fortuitous route to understanding, detecting and treating brain disease and injury.

History has shown us that flexible funding for innovative, risky projects is key for major scientific breakthroughs. I hope the latest round of "blue sky" initiatives will allow Picower Institute faculty to reach for the moon.

COVER:
Credit: David Mack / Science Source
Synapses. Computer artwork of synapses

New Insights Into How Brain Synapses Transmit Information

Throughout the animal kingdom, cells encapsulate molecules and proteins — that they move within or between — in tiny vesicles, which release their contents when they fuse with another membrane. Vesicles also package the chemical signals, or neurotransmitters, that leap from neuron to neuron in the brain's communication network, but neurons more tightly control the release of these signals. In schizophrenia, Parkinson's disease and other neurological disorders, however, this control breaks down, which may contribute to deficits in information processing. And researchers are seeking an explanation for the loss of the normal control mechanism.

Two new MIT studies now demonstrate how neurons have adapted the cell's standard fusion machinery to regulate the release of neurotransmitters at the neuron's chemical junctions called synapses.

"We show that an interplay between two proteins, complexin and synaptotagmin, controls the vesicle fusion machinery in neurons, and that both proteins are necessary to trigger normal information flow and prevent uncontrolled spontaneous release," says J. Troy Littleton, who led both studies and is an investigator in the Picower Institute for Learning and Memory and the Department of Biology and Department of Brain and Cognitive Sciences (BCS). The papers appear in the Dec. 2, 2012, and Jan. 2, 2013, issues of the Journal of Neuroscience.

Neurons have specialized needs, and one is to release neurotransmitters when the cell receives an electrical impulse that shoots down the axon to the synapses — typically in response to some stimulation. This impulse causes calcium to rush into the cell, which triggers the release of neurotransmitters across the synaptic gap to communicate with the next neuron. This neurotransmitter release is called an evoked response, as opposed to a spontaneous release (or "mini"), in which a small number of vesicles occasionally fuse without stimulation.

"So the first modification a neuron must make to the fusion machinery is to sense calcium," says Jihye Lee, a postdoctoral associate in the Littleton lab and first author of the Jan. 2 paper that examines the role synaptotagmin plays in calcium sensing.

Synaptotagmin is a protein localized to the neuronal vesicles, with two calcium-binding domains, C2A and C2B. Lee examined how each domain functions in this role. C2B drives the fast fusion of vesicles with the membrane, and requires C2A to dive into the membrane and activate the fusion machinery that promotes mixing of the two lipid membranes.

The second major requirement for neurons is to prevent these fusion events until a calcium signal arrives. Otherwise, neuronal signals flood the brain and wreak havoc, which leads to such neurological disorders as epilepsy. "We found that a protein known as complexin binds to the fusion machinery and prevents it from working until the calcium signal comes," says MIT affiliate Ramon Jorquera, first author of the Dec. 2 paper, which examines the interplay of complexin and synaptotagmin.

Complexin functions as a fusion clamp, keeping the vesicle from fusing with the synaptic membrane until synaptotagmin senses the influx of calcium and sets the extremely quick fusion process in motion.

This finding is important, Littleton says, because complexin is severely reduced in many neurological and psychological diseases, indicating these disease states may experience too many uncontrolled spontaneous release events. This reduction itself doesn't cause the diseases, but it may contribute to the phenotypes.

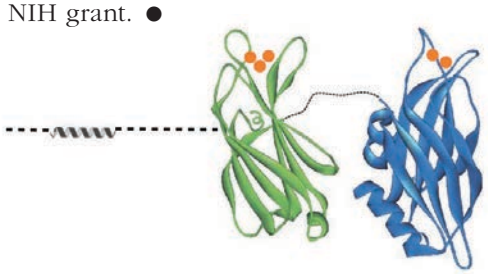
The researchers conducted these studies using the fruit fly, a valuable model organism because of the ease of doing genetic manipulations and neuronal recordings. They created flies in which they deleted or over-expressed various combinations of the genes for the complexin and synaptotagmin proteins, which determined the contribution of each to evoked and spontaneous neurotransmitter release. For example, deleting the complexin clamp caused a 100-fold increase in spontaneous minis; taking away the calcium-sensing synaptotagmin protein eliminated it all.

The researchers also focused on a type of synapse that is representative of the majority of synapses in the human central nervous system — those that release the excitatory neurotransmitter glutamate.

"Because this same machinery appears to play a similar role in mammals, we think we can gain valuable understanding about how it is controlled in humans too," Littleton says. "Our long-term goal is to learn how neurons normally talk to each other, and how this process goes awry during neurological and psychiatric diseases. This insight might ultimately allow us to restore proper synaptic function and brain communication in disease states."

Sarah Huntwork-Rodriguez, Yulia Akbergenova and Richard W. Cho, all of the Picower Institute, BCS and the Department of Biology, also contributed to the Dec. 2 paper. Their work was supported by a National Institutes of Health grant and the PEW Latin American Fellows Program in the Biomedical Sciences.

Akbergenova and Zhuo Guan, of the Picower Institute, BCS and the Department of Biology, also contributed to the Jan. 2 paper. This work was supported by an NIH grant. ●



Researchers Reverse Fragile X Syndrome Symptoms In Adult Mice

Neuroscientists at MIT's Picower Institute for Learning and Memory report in the March 18 Proceedings of the National Academy of Sciences (PNAS) that they have reversed autism symptoms in adult mice with a single dose of an experimental drug.

The work from the laboratory of Nobel laureate Susumu Tonegawa, the Picower Professor in the Department of Biology and a principal investigator at the Picower Institute, points to potential targets for drugs that may one day improve autism symptoms such as hyperactivity, repetitive behaviors and seizures in humans by modifying molecular mechanisms underlying the disease.

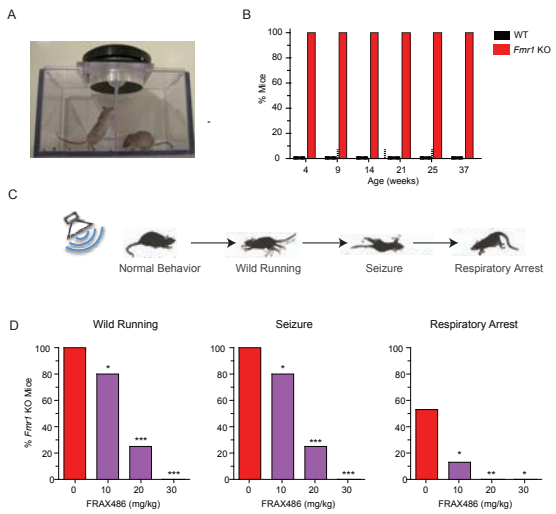
"These findings suggest a possible novel therapeutic target for the treatment of Fragile X Syndrome (FXS) — the most common inherited form of autism and intellectual disability," said Eric Klann, a professor of neural science at New York University.

Using genetically modified mice that exhibit FXS symptoms, the researchers targeted neurons' dendritic spines, small protrusions that receive signals from other neurons and are key to effective neuron-to-neuron communication within the brain. The researchers focused on spines in the temporal cortex, a part of the brain implicated in autism in humans.

Humans with FXS and autism, and the mouse model with FXS symptoms, have abnormally high densities of dendritic spines, leading to deficits in learning, cognition and behavior.

Tonegawa is scientific co-founder of Afraxis, a California-based company developing drugs that target p21-activated kinase or PAK, a key regulator of dendritic spines. Calling the inhibitor drug FRAX486, Tonegawa and colleagues demonstrated that inhibiting PAK with a single dose of FRAX496 reduced cellular and behavioral abnormalities in mice that model FXS.

This work was supported by the National Institutes of Health, the RIKEN Brain Science Institute and the Simons Center for the Social Brain at MIT. ●



In Search Of Better Antidepressants

A new study from researchers at MIT and Stanford University pinpoints brain cells that appear to be critically involved in depression, offering a possible target for new, more effective antidepressants.

By stimulating these cells to deliver dopamine to other parts of the brain, the researchers were able to immediately eliminate symptoms of depression in mice. They also induced depression in normal mice by shutting off the dopamine source.

The findings could help researchers develop antidepressants that are more precisely targeted, says Kay Tye, an assistant professor within the Department of Brain and Cognitive Sciences at MIT and one of the lead authors of a paper on the work appearing in the Dec. 12 online edition of Nature.

"The first step to achieving a new era of therapy is identifying targets like these," says Tye, who is a member of MIT's Picower Institute for Learning and Memory. "The fact that this target exists, I really hope it motivates drug companies to revitalize their neuroscience research groups."

Tye performed much of the research as a postdoc in the lab of Stanford professor Karl Deisseroth, the senior author of the paper. Other lead authors are Stanford research assistant Julie Mirzabekov and Stanford postdoc Melissa Warden.

FINDING TARGETS

Depression affects an estimated one in 10 Americans, many of whom receive drugs that boost the brain's chemical serotonin. However, these drugs (which include Prozac) require four to six weeks to have any effect. This suggests, Tye says, that serotonin may not be part of the brain system most responsible for depression-related symptoms.

"If serotonin was directly underlying the antidepressant effects of Prozac, then the very first day you take Prozac you should feel the effects, because that's what it's targeting immediately," she says. "The fact that it takes so long for the drug to work makes me think that the immediate effect of the drug itself is not having an antidepressant effect. When you have the drug in your system for a long time, the brain adapts, and the adaptation might actually be what is underlying the antidepressant effects of these drugs."

Finding more specific targets, rather than dousing the whole brain in chemicals, is key to developing better therapies, Tye says.

The researchers decided to investigate the dopamine system because it is known to play a major role in reward, motivation and pleasure. People suffering from depression often lack motivation, so dopamine has been considered a prime suspect in the disease. "Depressed patients will move around less, they have trouble getting out of bed, they don't enjoy things that they used to enjoy," Tye says.

Continued on p.5 »

Additionally, Parkinson's disease patients, who suffer from dramatically reduced dopamine levels that severely impair their movements, often experience depression before the complete onset of Parkinson's symptoms.

DOPAMINE CONTROL

For this study, the researchers used a relatively new technology known as optogenetics to selectively inhibit or stimulate dopamine-releasing neurons in the ventral tegmental area (VTA), which is a primary source of the brain's dopamine for reward and motivation.

Optogenetics allows scientists to control neurons' activity by genetically engineering them to express a light-sensitive protein that regulates the flow of ions in and out of the cell. Exposing these neurons to light turns them on or off nearly instantaneously. This offers a much more precise way of manipulating brain circuits than drugs, which can influence neighboring neurons and take more time to exert their effects.

In the first part of the study, the researchers turned off VTA dopamine-releasing neurons in normal mice. This immediately provoked depression-like symptoms, including a decline in motivation and the inability to feel pleasure.

Next, the researchers tested what would happen if they turned on VTA neurons in mice showing symptoms of depression. To generate depressive behavior, these mice were exposed to some type of mild stress twice a day for 10 weeks. Stressors included disruptions in circadian rhythms, social isolation, overcrowding or changes in temperature.

In humans, depression is often induced by similar patterns of low-grade but constant stress, Tye says.

This chronic mild stress is very different from severe acute stress, which can lead to post-traumatic stress disorder, Tye says. "It's more like a wearing away, where you don't really feel like you're in control. You never know what's going to happen. You just feel helpless as all these frustrating or annoying things happen."

When the researchers caused the VTA neurons in these mice to fire in bursts, flooding their brains with dopamine, the mice returned to normal behavior patterns within about 10 seconds.

Neurons in the VTA send dopamine to many different parts of the brain, but the researchers found that dopamine signals sent to the nucleus accumbens, known to play roles in reward, pleasure, fear and addiction, appear to have the most important role in controlling depression.

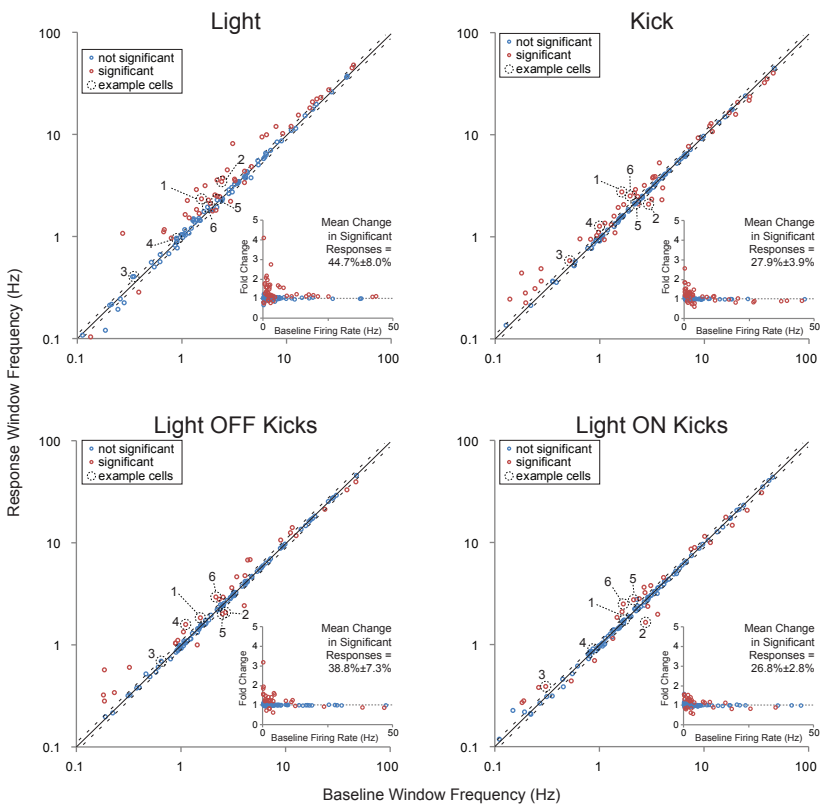
'A BIRD'S-EYE VIEW'

James Bibb, an associate professor of psychiatry at the University of Texas Southwestern Medical Center, says the new study represents a "tour de force of cutting-edge neuroscience."

"This gives us a completely new bird's-eye view of the critical synapses that will need to be targeted to more effectively treat mood disorders," says Bibb, who was not part of the research team. "Antidepressants represent the largest share of the mental-illness drug market and drug developers may very well use this information to come up with new and greatly needed treatments for those [who] suffer from major depressive disorder."

In her current research, Tye is looking for more new targets for antidepressants, both in the dopamine circuit studied in this paper and in other parts of the brain. She is also interested in examining how stress experienced early in life can influence health later on.

The research was funded by the Picower Institute Innovation Fund, the JPB Foundation, the Helen Hay Whitney Foundation, the Weigers Family Fund, the National Institute of Mental Health, the National Institute on Drug Abuse, the Defense Advanced Research Projects Agency, the Keck Foundation, the McKnight Foundation, the Gatsby Charitable Foundation, the Snyder Foundation, the Woo Foundation and the Albert Yu and Mary Bechman Foundation. ●



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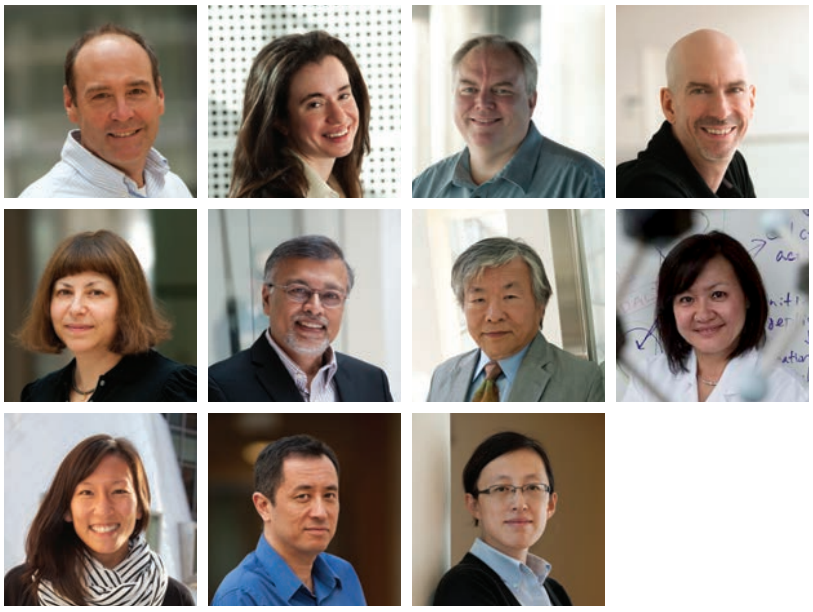

TOP ROW: Mark F. Bear, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Investigator, Howard Hughes Medical Institute (HHMI); Myriam Heiman, Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences, Broad Institute core member; Troy Littleton, Picower Professor of Biology and Neuroscience, Departments of Biology and Brain and Cognitive Sciences; Earl Miller, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences.

MIDDLE ROW: Elly Nedivi, Professor, Departments of Brain and Cognitive Sciences and Biology; Mriganka Sur, Paul E. Newton Professor of Neuroscience; Director of The Simons Center for the Social Brain; Susumu Tonegawa, Picower Professor of Biology and Neuroscience, Departments of Brain and Cognitive Sciences and Biology, Alumni Investigator, Howard Hughes Medical Institute, Alumni 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, Investigator, Howard Hughes Medical Institute.

BOTTOM ROW: Kay Tye, Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences, Matthew Wilson, Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology, Associate Director, The Picower Institute for Learning and Memory; Weifeng Xu, Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences.

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