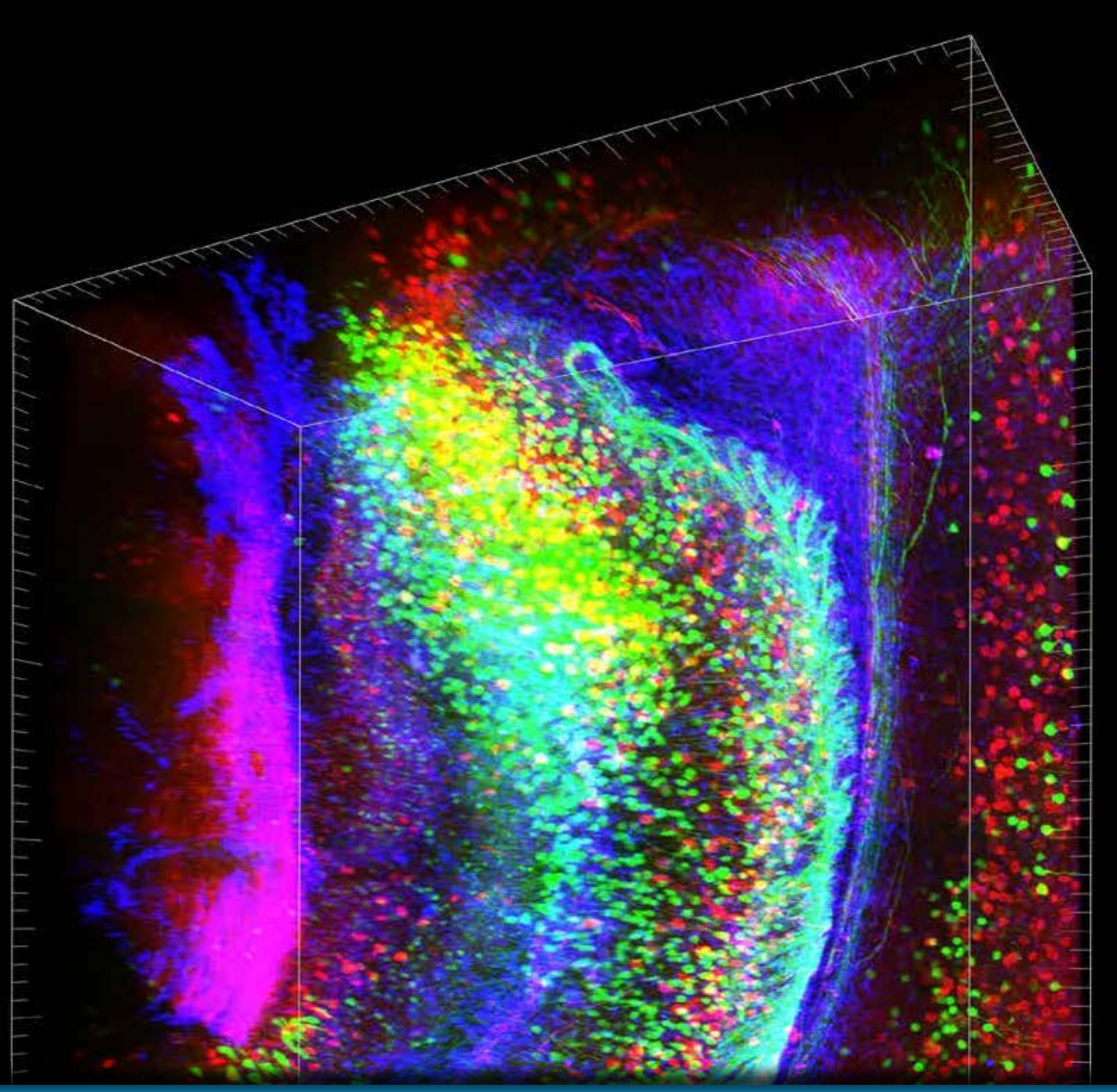


Neuroscience News

Fall 2013

THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY

Li-Huei Tsai

Director, Picower Institute for Learning and Memory

Photo / Azeddine Tahiri

FROM THE DIRECTOR
LI-HUEI TSAI

Earlier this year, we welcomed the newest member of our junior faculty—**Dr. Kwanghun Chung**. In a joint appointment, he was named assistant professor in Brain and Cognitive Sciences, assistant professor of Chemical Engineering, and a member of the Institute for Medical Engineering and Science at MIT. Kwanghun continues to study the cutting-edge technology he invented, called CLARITY, a methodology that rapidly transforms brain tissue into an optically transparent structure. He researches this and other new, innovative technologies that facilitate the study of neural circuitry to help guide the treatment of related neurodegenerative and neuropsychiatric diseases. He is committed to extending his experimental study of animals to groundbreaking discoveries in the human brain.

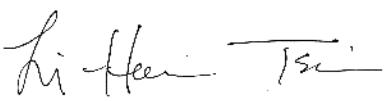
Kwanghun earned his undergraduate degree from Seoul National University, was awarded his doctorate from the Georgia Institute of Technology, and completed his postdoctoral training at Stanford University.

Another exemplary member of our junior faculty, **Dr. Kay Tye**—Picower principal investigator and assistant professor of Neuroscience in MIT's Department of Brain and Cognitive Sciences since January 2012—was recently awarded a 2013 National Institutes of Health (NIH) Director's New Innovator Award. The award supports creative new scientists who propose exceptionally innovative biomedical research ideas with high-impact potential. Kay has been studying the nervous system circuitry that regulates mood, emotion, and reward, exploring motivation, happiness and sadness, addiction, anxiety, and depression. She applies optogenetics and electrophysiology to analyze the underlying mechanisms of these behaviors. With the help of the NIH award, she is applying her innovative techniques to research our society's ongoing obesity epidemic.

Kay completed her undergraduate studies at MIT, earned her PhD at the University of California/San Francisco, and pursued her postdoctoral training at Stanford University.

The Picower Institute is wrapping up what has been a remarkable year, worthy of celebrating. We finish the year reflecting on significant accomplishments in recruiting phenomenal talent to our junior faculty, extraordinary scientific innovation, and unprecedented productivity in our vibrant neuroscience research community.

I wish all of you and your families Happy Holidays and continued success in the New Year!



Li-Huei Tsai, Ph.D.
Director

COVER:
An intact mouse brain stained with fluorescent labels for different proteins. Each color represents a different molecular label
Credit: Kwanghun Chung

HOW OLD MEMORIES FADE AWAY

If you got beat up by a bully on your walk home from school every day, you would probably become very afraid of the spot where you usually met him. However, if the bully moved out of town, you would gradually cease to fear that area.

Neuroscientists call this phenomenon "memory extinction": Conditioned responses fade away as older memories are replaced with new experiences.

A new study from MIT reveals a gene that is critical to the process of memory extinction. Enhancing the activity of this gene, known as Tet1, might benefit people with posttraumatic stress disorder (PTSD) by making it easier to replace fearful memories with more positive associations, says Li-Huei Tsai, director of MIT's Picower Institute for Learning and Memory.

The Tet1 gene appears to control a small group of other genes necessary for memory extinction. "If there is a way to significantly boost the expression of these genes, then extinction learning is going to be much more active," says Tsai, the Picower Professor of Neuroscience at MIT and senior author of a paper appearing in the Sept. 18 issue of the journal Neuron.

The paper's lead authors are Andrii Rudenko, a postdoc at the Picower Institute, and Meelad Dawlaty, a postdoc at the Whitehead Institute.

New and Old Memories

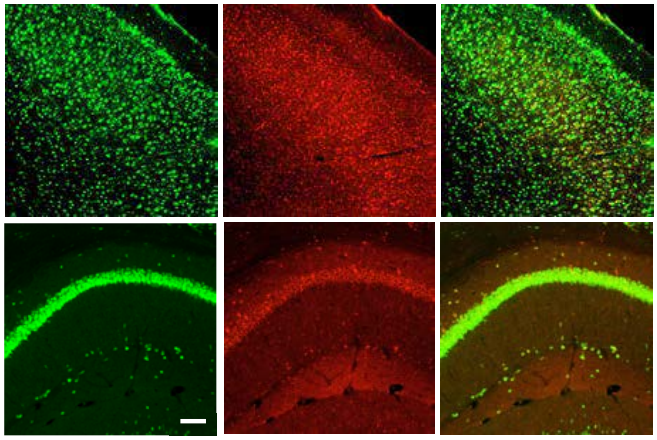
Tsai's team worked with researchers in MIT biology professor Rudolf Jaenisch's lab at the Whitehead to study mice with the Tet1 gene knocked out. Tet1 and other Tet proteins help regulate the modifications of DNA that determine whether a particular gene will be expressed or not. Tet proteins are very abundant in the brain, which made scientists suspect they might be involved in learning and memory.

To their surprise, the researchers found that mice without Tet1 were perfectly able to form memories and learn new tasks. However, when the team began to study memory extinction, significant differences emerged.

To measure the mice's ability to extinguish memories, the researchers conditioned the mice to fear a particular cage where they received a mild shock. Once the memory was formed, the researchers then put the mice in the cage but did not deliver the shock. After a while, mice with normal Tet1 levels lost their fear of the cage as new memories replaced the old ones.

"What happens during memory extinction is not erasure of the original memory," Tsai says. "The old trace of memory is telling the mice that this place is dangerous. But the new memory informs the mice that this place is actually safe. There are two choices of memory that are competing with each other."

In normal mice, the new memory wins out. However, mice lacking Tet1 remain fearful. "They don't relearn properly," Rudenko says. "They're kind of getting stuck and cannot extinguish the old memory."



Image/Andrii Rudenko

In another set of experiments involving spatial memory, the researchers found that mice lacking the Tet1 gene were able to learn to navigate a water maze, but were unable to extinguish the memory.

Control of Memory Genes

The researchers found that Tet1 exerts its effects on memory by altering the levels of DNA methylation, a modification that controls access to genes. High methylation levels block the promoter regions of genes and prevent them from being turned on, while lower levels allow them to be expressed.

Many proteins that methylate DNA have been identified, but Tet1 and other Tet proteins have the reverse effect, removing DNA methylation. The MIT team found that mice lacking Tet1 had much lower levels of hydroxymethylation — an intermediate step in the removal of methylation — in the hippocampus and the cortex, which are both key to learning and memory.

These changes in demethylation were most dramatic in a group of about 200 genes, including a small subset of so-called "immediate early genes," which are critical for memory formation. In mice without Tet1, the immediate early genes were very highly methylated, making it difficult for those genes to be turned on.

In the promoter region of an immediate early gene known as Npas4 — which Yingxi Li, the Frederick A. and Carole J. Middleton Career Development Assistant Professor of Neuroscience at MIT, recently showed regulates other immediate early genes — the researchers found methylation levels close to 60 percent, compared to 8 percent in normal mice.

"It's a huge increase in methylation, and we think that is most likely to explain why Npas4 is so drastically downregulated in the Tet1 knockout mice," Tsai says.

"By demonstrating some of the ways that regulatory genes are methylated in response to Tet1 knockout and behavioral experience, the authors have taken an important step in identifying potential pharmacological treatment targets for disorders such as PTSD and

addiction," says Matthew Lattal, an associate professor of behavioral neuroscience at Oregon Health and Science University, who was not part of the research team.

Keeping Genes Poised

The researchers also discovered why the Tet1-deficient mice are still able to learn new things. During fear conditioning, methylation of the Npas4 gene goes down to around 20 percent, which appears to be low enough for the expression of Npas4 to turn on and help create new memories. The researchers suspect the fear stimulus is so strong that it activates other demethylation proteins — possibly Tet2 or Tet3 — that can compensate for the lack of Tet1.

During the memory-extinction training, however, the mice do not experience such a strong stimulus, so methylation levels remain high (around 40 percent) and Npas4 does not turn on.

The findings suggest that a threshold level of methylation is necessary for gene expression to take place, and that the job of Tet1 is to maintain low methylation, ensuring that the genes necessary for memory formation are poised and ready to turn on at the moment they are needed.

The researchers are now looking for ways to increase Tet1 levels artificially and studying whether such a boost could enhance memory extinction. They are also studying the effects of eliminating two or all three of the Tet enzymes.

"This will not only help us further delineate epigenetic regulation of memory formation and extinction, but will also unravel other potential functions of Tets and methylation in the brain beyond memory extinction," Dawlaty says.

The research was funded by the National Institutes of Health, the Simons Foundation and the Howard Hughes Medical Institute. ●

BRAIN CIRCUIT CAN TUNE ANXIETY

Anxiety disorders, which include posttraumatic stress disorder, social phobias and obsessive-compulsive disorder, affect 40 million American adults in a given year. Currently available treatments, such as antianxiety drugs, are not always effective and have unwanted side effects.

To develop better treatments, a more specific understanding of the brain circuits that produce anxiety is necessary, says Kay Tye, an assistant professor of brain and cognitive sciences and member of MIT's Picower Institute for Learning and Memory.

"The targets that current antianxiety drugs are acting on are very nonspecific. We don't actually know what the targets are for modulating anxiety-related behavior," Tye says.

In a step toward uncovering better targets, Tye and her colleagues have discovered a communication pathway between two brain structures — the amygdala and the ventral hippocampus — that appears to control anxiety levels. By turning the volume of this communication up and down in mice, the researchers were able to boost and reduce anxiety levels.

Lead authors of the paper, which appears in the Aug. 21 issue of Neuron, are technical assistant Ada Felix-Ortiz and postdoc Anna Beyeler. Other authors are former research assistant Changwoo Seo, summer student Christopher Leppla and research scientist Craig Wildes.

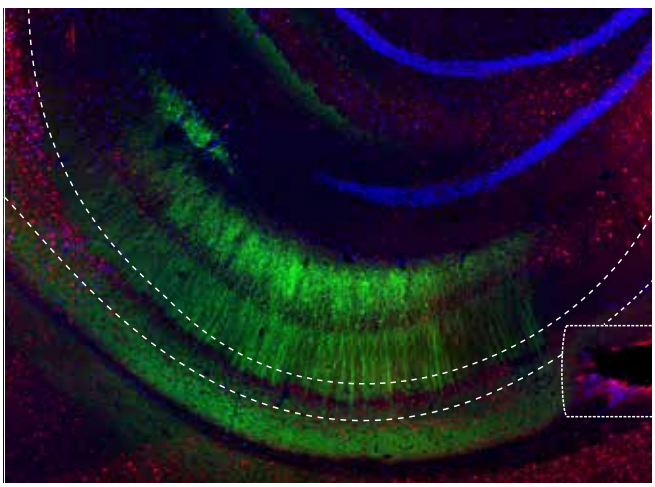
Measuring Anxiety

Both the hippocampus, which is necessary for memory formation, and the amygdala, which is involved in memory and emotion processing, have previously been implicated in anxiety. However, it was unknown how the two interact.

To study those interactions, the researchers turned to optogenetics, which allows them to engineer neurons to turn their electrical activity on or off in response to light. For this study, the researchers modified a set of neurons in the basolateral amygdala (BLA); these neurons send long projections to cells of the ventral hippocampus.

The researchers tested the mice's anxiety levels by measuring how much time they were willing to spend in a situation that normally makes them anxious. Mice are naturally anxious in open spaces where they are easy targets for predators, so when placed in such an area, they tend to stay near the edges.

When the researchers activated the connection between cells in the amygdala and the hippocampus, the mice spent more time at the edges of an enclosure, suggesting they felt anxious. When the researchers shut off this pathway, the mice became more adventurous and willing to explore open spaces. However, when these mice had this pathway turned back on, they scampered back to the security of the edges.



Image/Ada Celis Felix-Ortiz

Complex Interactions

In a study published in 2011, Tye found that activating a different subset of neurons in the amygdala had the opposite effect on anxiety as the neurons studied in the new paper, suggesting that anxiety can be modulated by many different converging inputs.

"Neurons that look virtually indistinguishable from each other in a single region can project to different regions and these different projections can have totally opposite effects on anxiety," Tye says. "Anxiety is such an important trait for survival, so it makes sense that you want some redundancy in the system. You want a couple of different avenues to modulate anxiety."

The Neuron study contributes significantly to scientists' understanding of the roles of the amygdala and hippocampus in anxiety and offers directions for seeking new drug targets, says Joshua Gordon, an associate professor of psychiatry at Columbia University.

"The study specifies a particular connection in the brain as being important for anxiety. One could imagine, then, identifying components of the machinery of that connection — synaptic proteins or ion channels, for example — that are particularly important for amygdala-hippocampal connectivity. If such specific components could be identified, they would be potential targets for novel antianxiety drugs," says Gordon, who was not part of the research team.

In future studies, the MIT team plans to investigate the effects of the amygdala on other targets in the hippocampus and the prefrontal cortex, which has also been implicated in anxiety. Deciphering these circuits could be an important step toward finding better drugs to help treat anxiety.

The research was funded by the JPB Foundation, the Picower Institute Innovation Fund, the Whitehall Foundation and the Klingenstein Foundation. ●

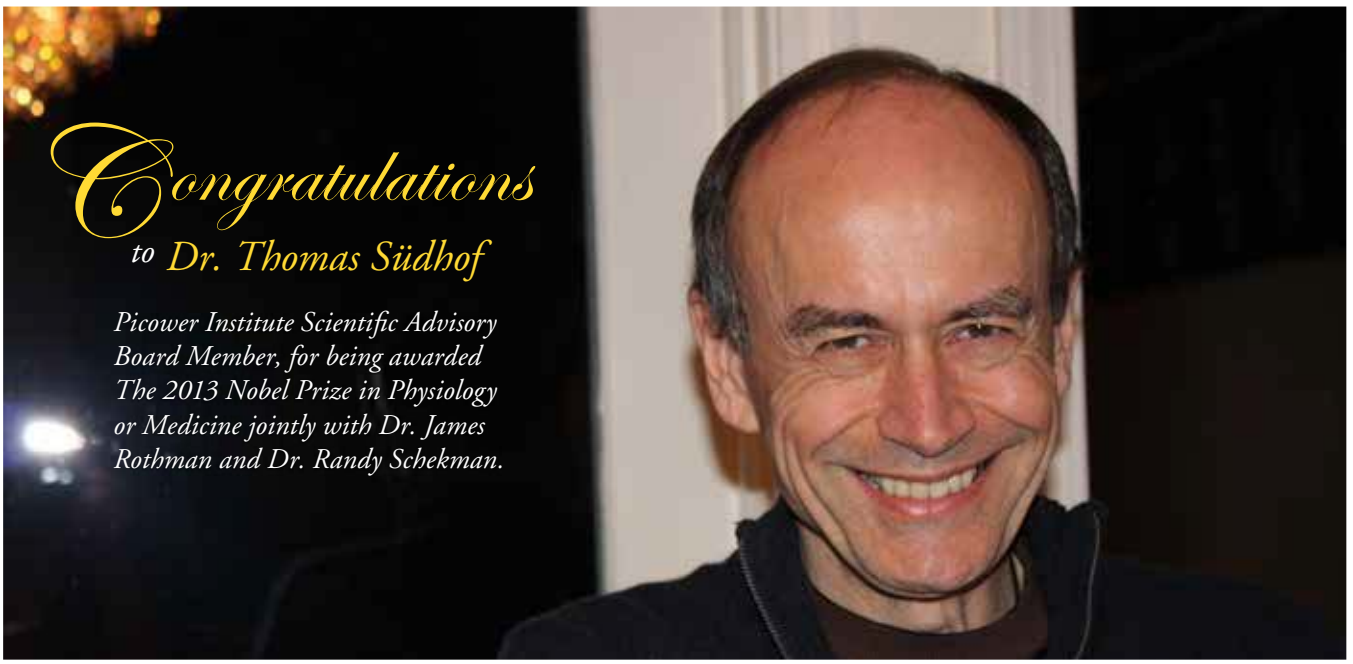
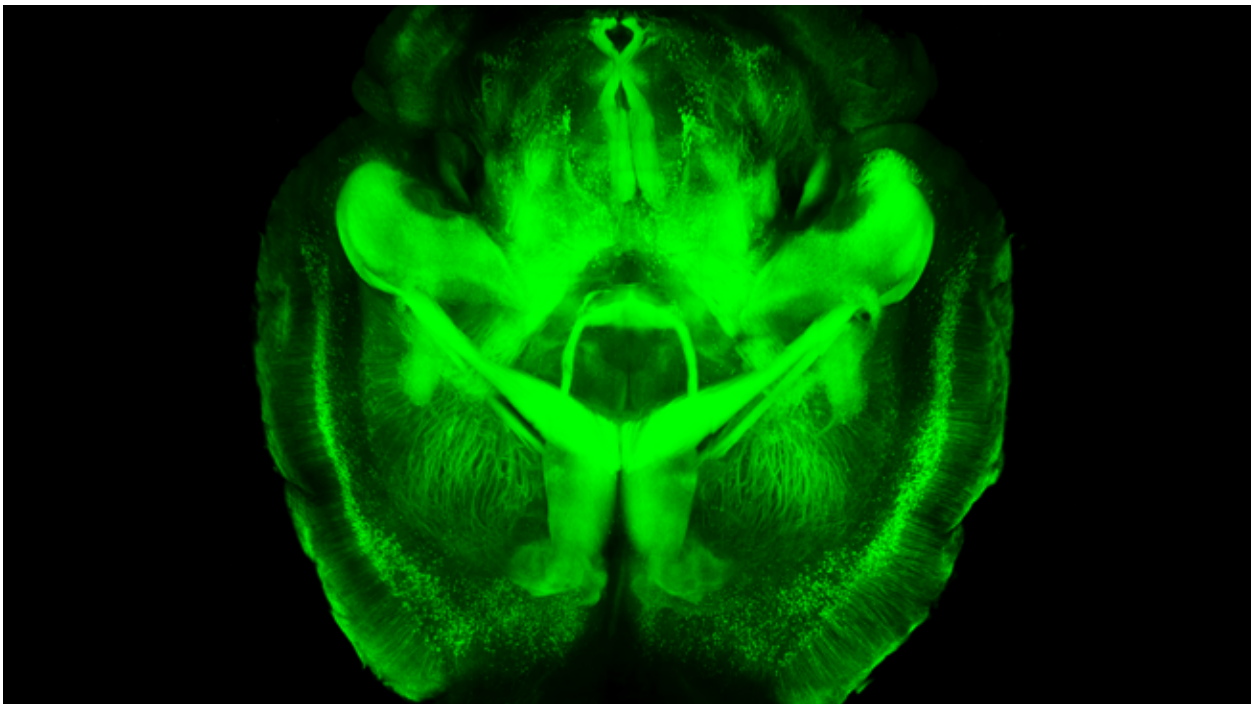


Photo: courtesey of Dr. Thomas Sudhof.

Announcements

- Our own Scientific Advisory Board Member Dr. Thomas Sudhof was awarded the The 2013 Nobel Prize in Physiology or Medicine jointly with Dr. James Rothman and Dr. Randy Schekman.
- Dr. Kay Tye, was awarded the NIH New Innovator Award and plans to study the obesity epidemic from the source of the problem: the compulsive consumption of unhealthy food, such as those high in sugar.
- Our iPS Core Facility is now offering its services to Boston area hospitals and universities.
- New monthly Bioinformatics Workshops are now being offered to the Picower Community on a regular basis by staff member Dr. Fan Gao.



One day in 2011, Kwanghun Chung, while a post-doc at Stanford, put half a mouse brain on top of the label of a container of saline solution and showed everyone in the lab how they could read the label right through the tissue.

Chung had invented a chemical treatment that keeps organs intact while rendering them transparent.

CLARITY, as its creators call it, has been called one of the most important advances for neuroanatomy in decades. Its possibilities--tracing specific neural circuits, illuminating cells and subcellular structures, exploring how proteins, nucleic acids and neurotransmitters interact, for starters--extend far beyond labor-intensive, error-prone reconstructions of two-dimensional brain slices.

Chung, known as KC, joined MIT this year. In addition to his appointment as a Picower principal investigator, he is building a lab as an assistant professor for the Institute for Medical Engineering and Science (IMES) and the Department of Chemical Engineering.

There's a palpable buzz about CLARITY. A handful of labs in the UK and the US are already experimenting with making see-through brains. A recent workshop at the Picower Institute led by members of the Chung lab drew participants from Princeton, Harvard, the University of Utah, as well as labs within MIT. "We want to train people to use this technology for their research," Chung said.

A Clear View

While it's been known for decades that lipids are the culprit that renders brains opaque, simply removing the lipids turns the tissue into soup, Chung said. His unique approach is to replace the lipids with the kind of transparent hydrogel commonly used in biology to separate and study proteins.

After a sample brain is zapped with an electrical charge and fixed with formaldehyde, it sits for days in a hydrogel bath that, when heated to around body temperature, forms a mesh that holds the tissue together but doesn't bind to lipids. The lipids are then washed away with detergent.

Fluorescently labeling neurons, axons, dendrites, synapses, proteins, nucleic acids, layers of the cortex or inner structures of the brain illuminates them; commercially available software renders the data in 3D and you're left with a spectacular light show in a box, where a subset of astrocytes, excitatory neurons, and inhibitory neurons are represented by brilliant blues, greens, and smears of pink. The excitatory neurons undulate like green cilia or hair-thin fiber-optic cables with glowing neon tips.

Chung hopes to use CLARITY to see physical and chemical differences between diseased brains and healthy brains. "We don't know which components and circuits are abnormal in many brain disorders. In Alzheimer's and Parkinson's, specific types of neurons die; while others–the same cell type in the same brain region–are fine. There are so many things we don't know about neurodegenerative and neurodevelopmental disorders," he said. "I want to pinpoint those abnormal components to help us understand the underlying mechanisms and develop new therapeutic strategies. This technique helps us extract more complete information from the brain." ●








Photos credits: Azeddine Tahiri - Tahiri Media

THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY

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

Neuroscience News

Fall 2013

TOP ROW: Mark F. Bear, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Investigator, Howard Hughes Medical Institute (HHMI); Kwanghun Chung, Assistant Professor, Departments of Chemical Engineering and Brain and Cognitive Sciences. 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.
MIDDLE ROW: Earl Miller, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences; 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, Investigator, Howard Hughes Medical Institute, Investigator and Director of the RIKEN-MIT Center for Neural Circuit Genetics.
BOTTOM ROW: 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. 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.

How to Subscribe

Subscriptions to *Neuroscience News*, the quarterly newsletter of the Picower Institute for Learning and Memory, are available at no charge in print or PDF form. To subscribe, send your mailing or email address to:

Neuroscience News
najatk@mit.edu

How to Submit

News, story ideas and comments from readers are welcome. Please contact Najat Kessler, at najatk@mit.edu.

Support the Picower Institute

For more information on our research or how to make a gift to the Picower Institute for Learning and Memory, please contact:

Office of the Director
Tel: 617-324-1660
Email: lhtsai@mit.edu

Contact the Picower Institute

MIT
The Picower Institute for Learning and Memory
Massachusetts Institute of Technology
77 Massachusetts Avenue, Building 46, Room 1303
Cambridge, MA 02139-4307

Tel: 617-324-0305
picower.mit.edu
Editorial Board: Najat Kessler & David Vaughn