



MCGOVERN INSTITUTE

FOR BRAIN RESEARCH AT MIT

# Brain SCAN

WINTER 2012 ■ Issue no. 22

---

**Yingxi Lin**

*Searching for the molecular basis of learning  
and memory*



## FROM THE DIRECTOR

In this issue we feature Yingxi Lin, who joined the McGovern faculty in 2009 and has just published her first paper from her own lab.

This is an important milestone for any new investigator and is especially exciting in Yingxi's case because it is such an impressive study – combining genetics, molecular biology, and behavioral testing to dissect the molecular control of memory formation. We also congratulate Yingxi on a personal milestone, the birth of her daughter Tallis, who is now providing her parents with a unique opportunity to appreciate the miracle of brain plasticity!

I am also delighted to announce that Rebecca Saxe has joined the McGovern Institute as an associate member. Rebecca is truly a star, among the most talented and creative scientists of her generation. Her main interest is the neural basis of human social cognition – a topic with far-reaching implications for understanding empathy, conflict, and perhaps even the origins of autism.

Finally, I'm pleased to report on three new gifts to the institute. One of these will create a new named professorship, while the other two will support a range of disease-related projects. As always, my sincerest thanks to each of these donors and to all who have chosen to support our work.

**Bob Desimone, Director**

*On the cover:  
Mouse hippocampus, labeled with genetic markers.*

*Image courtesy of Tamily Weissman and Jeff Lichtman; details on our website.*

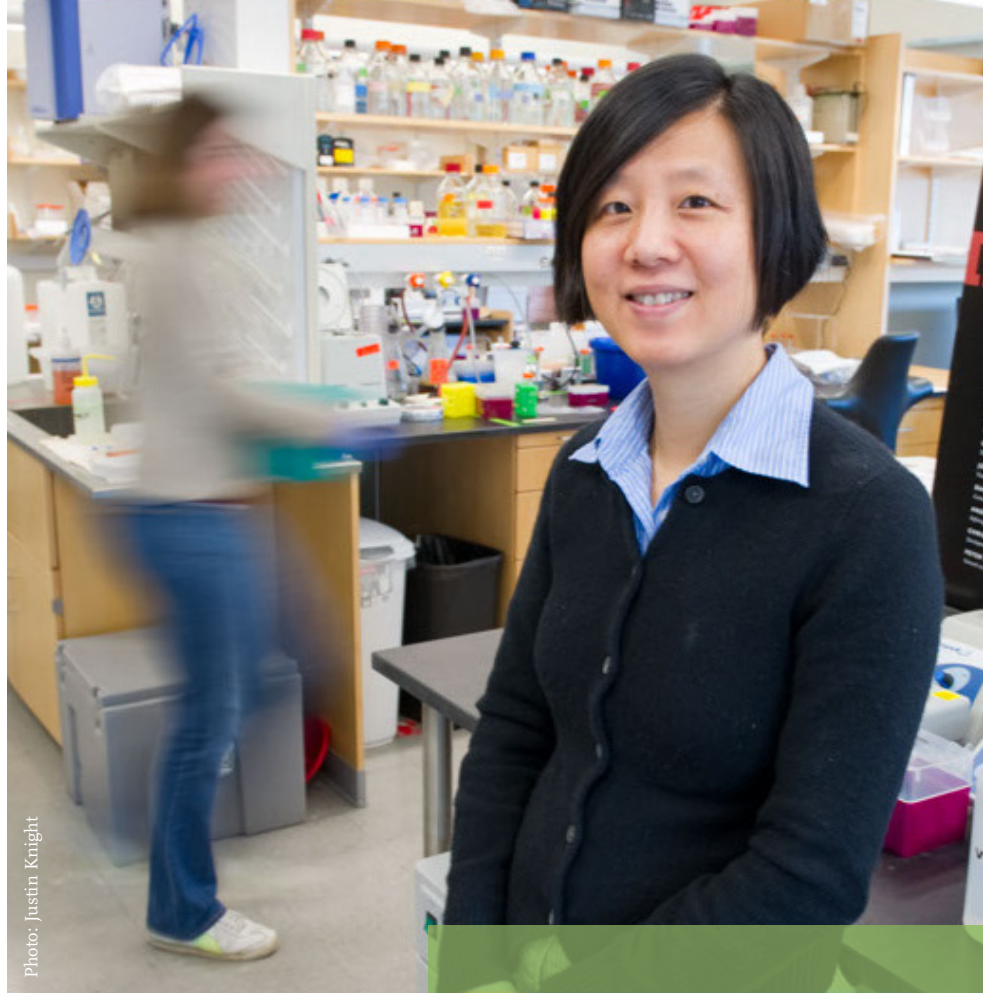


Photo: Justin Knight

## Yingxi Lin uses genetics, electrophysiological methods and behavioral testing to understand how new memories are formed within the brain.

When Yingxi Lin runs into old college friends from China, she baffles them with news that she's a neuroscientist. "Um, you're a what?" they say.

Their confusion is understandable. Lin, the Fred and Carole Middleton Career Development Professor in the Department of Brain and Cognitive Sciences, had studied engineering physics as an undergraduate, and when she left China, her plans for



# Yingxi Lin

*Searching for the molecular basis of learning and memory*

study did not include brain science. “I was thinking I would either do high energy physics or medical physics,” she says. “To be honest,” she adds, lowering her voice and laughing, “I hated biology.”

Part of the problem was that her high school biology classes, which focused on memorization and categorization, seemed static when compared with the dynamics of chemical reactions or the physics of motion and energy. “I wasn’t interested in biology at all,” she says. It just wasn’t fascinating enough.

And if there is a single driving force behind Lin’s career, it is her own fascination. When a question intrigues her, she searches for ways to explore it. Ultimately, this path has led her from engineering physics to the forefront of neuroscience, where she is now working to understand the molecular underpinnings of how memories form and persist deep inside the brain.

## Making Connections

As an example of what she calls her “not so straight-line path,” Lin decided while she was a physics graduate student at Harvard to take a class on magnetic resonance imaging (MRI). At that time, the use of MRI in medicine was expanding rapidly, but Lin learned that the same underlying physical principle, known as nuclear magnetic resonance (NMR), could also be used to look at the atomic structures of cellular proteins.

Something clicked. Her expertise in physics had applications that had never occurred to her before: In the deepest biological places, molecules interact to make life unfold.

Lin decided to learn more, so she joined the lab of Gerhard Wagner, a structural biologist at Harvard Medical School who was using NMR to solve protein structures.



*Lin studied engineering physics as an undergraduate at Tsinghua University in Beijing.*

Wagner, also a physicist by training, introduced Lin to molecular biology. She studied transcription factors, proteins that control the activity of genes and thus the responses of cells to their surrounding environment. “Wow,” Lin remembers thinking. “I hadn’t realized that biology could be so interesting.”

She was hooked, and for her postdoc work she decided to dive into molecular neurobiology. In 2001 she applied to the lab of Michael Greenberg, a neuroscientist at Children’s Hospital Boston. Despite stiff competition for positions in the lab, he agreed to take her. “I was very inexperienced, but I was meticulous and quantitative and it was a supportive lab,” says Lin. “I ended up having great mentors.”

### Feedback Loops

In Greenberg’s lab, Lin explored the molecular mechanisms that shape the brain’s wiring, focusing specifically on the formation of inhibitory synapses. In the brain, signals pass from one neuron to another through synaptic connections. A neuron sends an electrical pulse along a thread-like axon until it reaches a

synapse, where it triggers the release of a chemical signal that spreads to other nearby neurons. In many cases, this signal is a neurotransmitter called glutamate, which stimulates the activity of the receiving neurons. However, other synapses release a different transmitter called GABA, which produces the opposite effect, inhibiting the activity of its downstream target neurons.

***“To sustain a life in research, you have to work on something that captures your imagination.”***

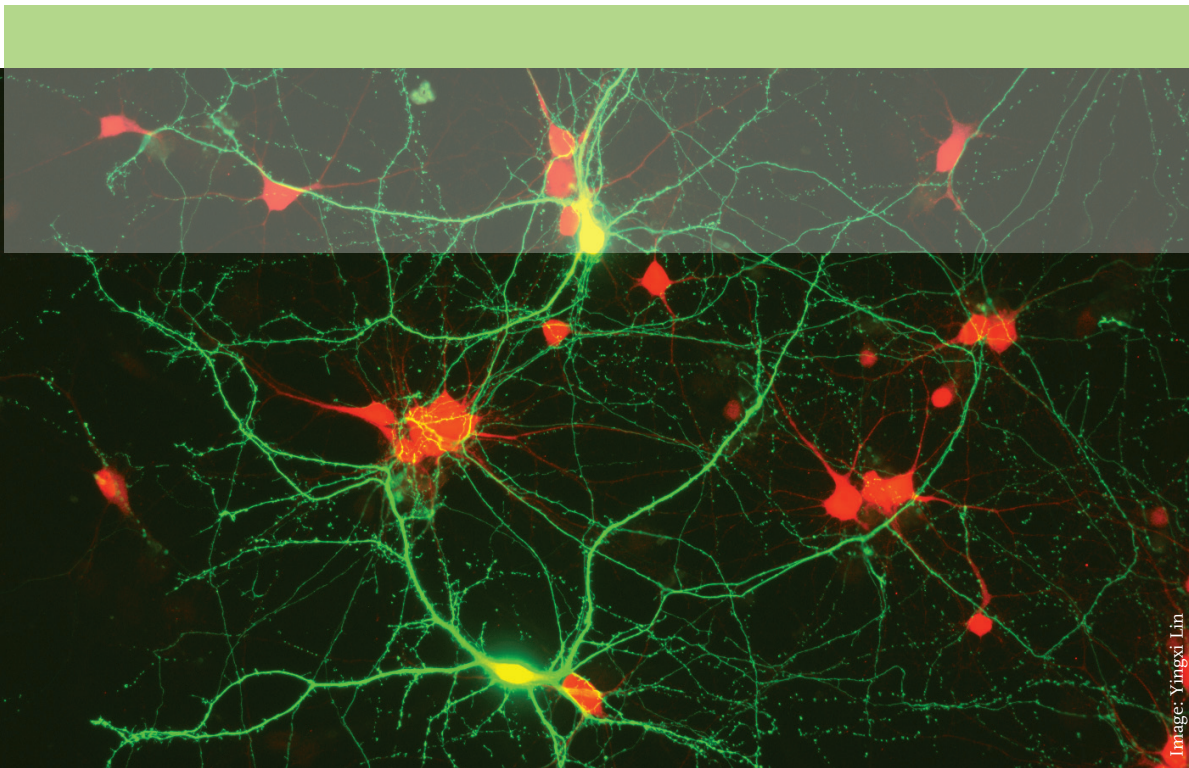
— *Yingxi Lin*

As the brain experiences the world, it tunes this wiring. If the brain fails to develop the right balance between excitatory and inhibitory signals, it cannot function properly. Autism, schizophrenia, and epilepsy have all been associated with an imbalance between these connections, though prior to Lin’s work, little was known about how the brain finds the proper balance between excitation and inhibition.

Lin and Greenberg decided to take a genetic approach. Electrical activity was known to affect the development of synapses, so they began a search for genes whose expression was altered when neurons became more electrically active. In particular, they speculated that activity-dependent changes in gene expression might be important in controlling the formation of inhibitory synapses.

The idea made sense from an engineering perspective. “We were looking for a negative feedback mechanism,” explains Lin. “If a neuron starts to become overactive, you want to make more inhibitory synapses to maintain the balance between excitation and inhibition.”

Progress was slow at first, but her persistence paid off when she and Greenberg found that a gene called *Npas4* is regulated by neuronal activity and involved in the process of building inhibitory synapses. They were especially excited by the fact that *Npas4* is a transcription factor – a controller of other genes – and so might be a “master switch” for triggering the neuron’s response to activity. In 2008 they published their findings in the prestigious journal *Nature*, and Lin was offered a faculty position at the McGovern Institute.



*The Lin lab uses cultured neurons to study how the brain forms new memories as a result of experience.*

Image: Yingxi Lin



Photo: Justin Knight

Lin with graduate student Kartik Ramamoorthi.

## Memories

In her own lab at MIT, Lin has continued to study the link between electrical activity and gene expression, but she also wants to understand what it might mean for behavior. “That’s what brains do, right?” says Lin, who is watching this process unfold today in her newborn daughter. “We sometimes watch her and joke, maybe *Npas4* is turned on right now. It’s fascinating!”

Lin decided to explore whether inhibitory synapses play a role in learning and memory. To pursue this project, Lin recruited Kartik Ramamoorthi, now a second-year graduate student. They began with a form of learning known as contextual fear conditioning, in which mice are allowed to wander in a specific chamber and are then jolted with a mild electric

shock. Within minutes, the mice learn to recognize the shock-rigged chamber and to freeze in fear the next time they enter it.

Using molecular tools, Lin and Ramamoorthi found that *Npas4* appears to act as a “master switch” that turns on the formation of this memory. Moreover, they were able to localize this effect to the hippocampus – a brain structure known to be essential for human memory, and a prime target for degeneration in Alzheimer’s disease. Their study, published in *Science*, is an important step toward understanding the molecular pathway that underlies fast learning.

Now they hope to label the cells that have activated *Npas4* in response to a specific experience, determine whether these cells encode the memory and, if so, identify the changes within those cells that allow the memory to persist. “I look at it as a way to zoom into the brain,” says Lin. “If we think information is encoded in a certain group of cells, we need to go in and test it.”

Ramamoorthi adds, “Yingxi has this incredible ability to step back and understand which experiments we need to do to tie together our key observations.”

## Risk and Reward

Lin had taken a chance on Ramamoorthi. When they met, he had been studying learning and memory as an undergraduate at Rutgers University. Aiming to go to graduate school, but too inexperienced to dive right in, he signed on as a research technician and helped Lin set up her new lab at the McGovern Institute. He has since been accepted into the MIT graduate program, where he has chosen to remain in Lin’s lab. “She let me pursue this novel idea which has worked out great for both of us,” he says. “In that sense she’s pretty fearless, which is unique.”

For Lin, taking risks is an inherent part of science. “Science is very chancy, and you will fail many times,” says Lin. “You have to work on something that captures your imagination. If you don’t have a burning desire, you may not be able to sustain a life in research.”

On top of all of that, you have to be very good. That, to Lin, means working hard and having a deep understanding of all that you do. Now a mentor herself, these are the key lessons she brings to her graduate students. “These two qualities equate to preparation,” says Lin, “so that when opportunity arises, you can seize it.” ■

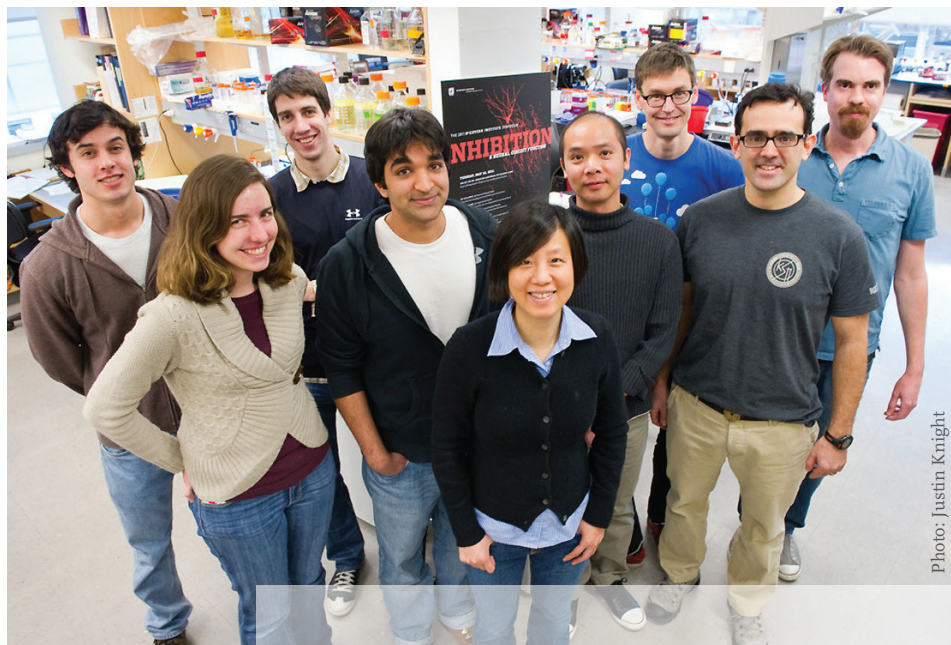


Photo: Justin Knight

Since she joined the McGovern faculty in 2009, Yingxi Lin’s lab has grown to eight members.

**March 14 at 7pm**

Autism Speaks Science Panel  
with Guoping Feng  
*Boston Public Library*

**April 19 at 4pm**

Scolnick Prize Lecture  
Speaker: Roger Nicoll, UCSF  
*MIT Bldg 46-3002*

**April 27 from 8am-5pm**

McGovern Symposium  
“Magnetoencephalography  
and cognitive neuroscience”  
*MIT Bldg 46-3002*

## Gifts to Institute Will Support Professorship, Disease Research

Donna and Chuck Hieken '51 have made a generous gift to support Alzheimer's disease research at the McGovern Institute. Chuck, a principal at the law firm of Fish and Richardson PC, and Donna, a flutist, have a strong interest in this neurodegenerative disease, and their gift will support a wide range of projects at the institute.

A gift from Michael Boylan '54 of Houston, Texas, will support the work of McGovern researcher Feng Zhang. Mike was inspired by a visit to the institute, during which he learned about Zhang's work on new technologies for studying neuropsychiatric diseases. Zhang joined the institute in 2011, and this gift will provide critical seed funding to support his lab in its early years.

Phyllis and Glen Dorflinger '46, MIT supporters for over six decades, have designated their MIT charitable remainder trust to benefit the McGovern Institute.



A gift from Donna and Chuck Hieken '51 will support Alzheimer's research.

Their gift will create a named professorship in neuroscience. Sadly, Glen passed away in September, a few weeks after his visit to the institute. ■

## Gift Will Boost Autism Research at MIT

McGovern researchers will be among the beneficiaries of a major new gift to support autism research at MIT. The Simons Foundation will donate \$26.5 million to establish a new center, focused on understanding the brain basis of social behavior and its disruption in autism spectrum disorders. It will support a wide range of basic and translational research projects, including a contribution toward a new MRI scanner (*next story*). ■



Modern MRI scanners can reveal the structure and function of the human brain with unprecedented detail.

## New MRI Scanner Within Reach

The Martinos Imaging Center hopes soon to acquire a new magnetic resonance imaging (MRI) scanner. The instrument, with an estimated cost of \$3 million, will support a wide range of projects aimed at understanding normal human brain function in children and adults, as well as the basis and possible treatment of many brain disorders. Within the past few months, two gifts—\$1 million from the Simons Foundation and \$1.5 million from an anonymous donor—have brought us substantially closer to our goal.

To learn more about our plans for the new MRI scanner, contact Kara Flyg at [kflyg@mit.edu](mailto:kflyg@mit.edu) or 617-324-0134. ■

## Synaptic Physiologist to Receive Scolnick Prize

The McGovern Institute will award the 2012 Scolnick Prize to Roger Nicoll of the University of California, San Francisco. Nicoll is one of the world's foremost experts on synaptic plasticity, the process by which the brain's connections are modified in response to experience. His prize lecture is scheduled for April 19 at 4pm. ■



Roger Nicoll, winner of the 2012 Scolnick Prize.

## McGovern Institute Welcomes New Associate Member

We are delighted to announce that Rebecca Saxe has joined the McGovern Institute as an associate member. Saxe, a faculty member in MIT's Department of Brain and Cognitive Sciences, is best known for her work on a human brain region that is specialized for "theory of mind" tasks that involve understanding the mental states of other people. Although it was known previously that the brains of humans and animals have regions that are specialized for basic functions such

as vision and motor control, this was the first example of a brain region specialized for high-level social cognition.

Saxe has found that this "theory of mind" region is involved when we make moral judgments about other people's behavior. She is also studying its possible role in autism, a condition in which the ability to understand other people's beliefs and motivations is often impaired. ■



Rebecca Saxe studies how we think about other people's thoughts.

## RESEARCH NEWS



**Michale Fee** studies how birds learn to sing – a model for understanding how humans learn spoken language and other skills requiring complex movements. In a new study he found that the immature birds' songs, which resemble babies' babbling, consist of a mixture of stereotypic and random sounds, each of which is controlled by different brain circuits.

**Yingxi Lin's** lab has identified a key gene involved in memory formation (*see page 2*).

**Feng Zhang, Guoping Feng** and colleagues reported an improved method for making customized DNA-binding proteins known as TALEs. The method, which will allow researchers to 'edit' DNA in living cells, is expected to find many applications in biomedical research.

**Rebecca Saxe** published two related papers on the neurobiology of empathy. The first identifies brain regions that respond to the suffering of other people. The second examines how these responses differ when subjects are drawn from opposite sides of ethnic conflicts. ■

# AWARDS AND HONORS

**Ed Boyden, Bob Horvitz, Nancy Kanwisher, and Tomaso Poggio** were among 12 MIT faculty invited to speak at the 2012 World Economic Forum in Davos, Switzerland.

**Ed Boyden** is the first recipient of the Institution of Engineering and Technology's A F Harvey Prize. The prize is awarded in recognition of outstanding contributions to research in medical engineering. Boyden's optogenetic technology was also featured in *Wired Magazine's* "25 Big Ideas for 2012."

**Feng Zhang** has received the Damon Runyon-Rachleff Innovation Award, which supports the "next generation of exceptionally creative thinkers with high risk/high reward ideas." ■



*Davos, Switzerland, where four McGovern faculty members spoke at the World Economic Forum.*

■ *The McGovern Institute for Brain Research at MIT is led by a team of world-renowned neuroscientists committed to meeting two great challenges of modern science: understanding how the brain works and discovering new ways to prevent or treat brain disorders. The McGovern Institute was established in 2000 by Patrick J. McGovern and Lore Harp McGovern, who are committed to improving human welfare, communication and understanding through their support for neuroscience research. The director is Robert Desimone, formerly the head of intramural research at the National Institute of Mental Health.*

*Further information is available at: <http://mcgovern.mit.edu>*

■ **Brain SCAN**  
Quarterly  
■ Newsletter of  
■ the McGovern  
■ Institute

**Editors:** Charles Jennings, Julie Pryor  
**Writer:** Elizabeth Dougherty  
**Director of Development:** Kara Flyg  
**Design:** Sametz Blackstone Associates, Boston

■ © Copyright 2012, McGovern Institute for Brain Research at MIT



**MCGOVERN INSTITUTE**

FOR BRAIN RESEARCH AT MIT

Massachusetts Institute of Technology  
77 Massachusetts Avenue 46-3160  
Cambridge, MA 02139