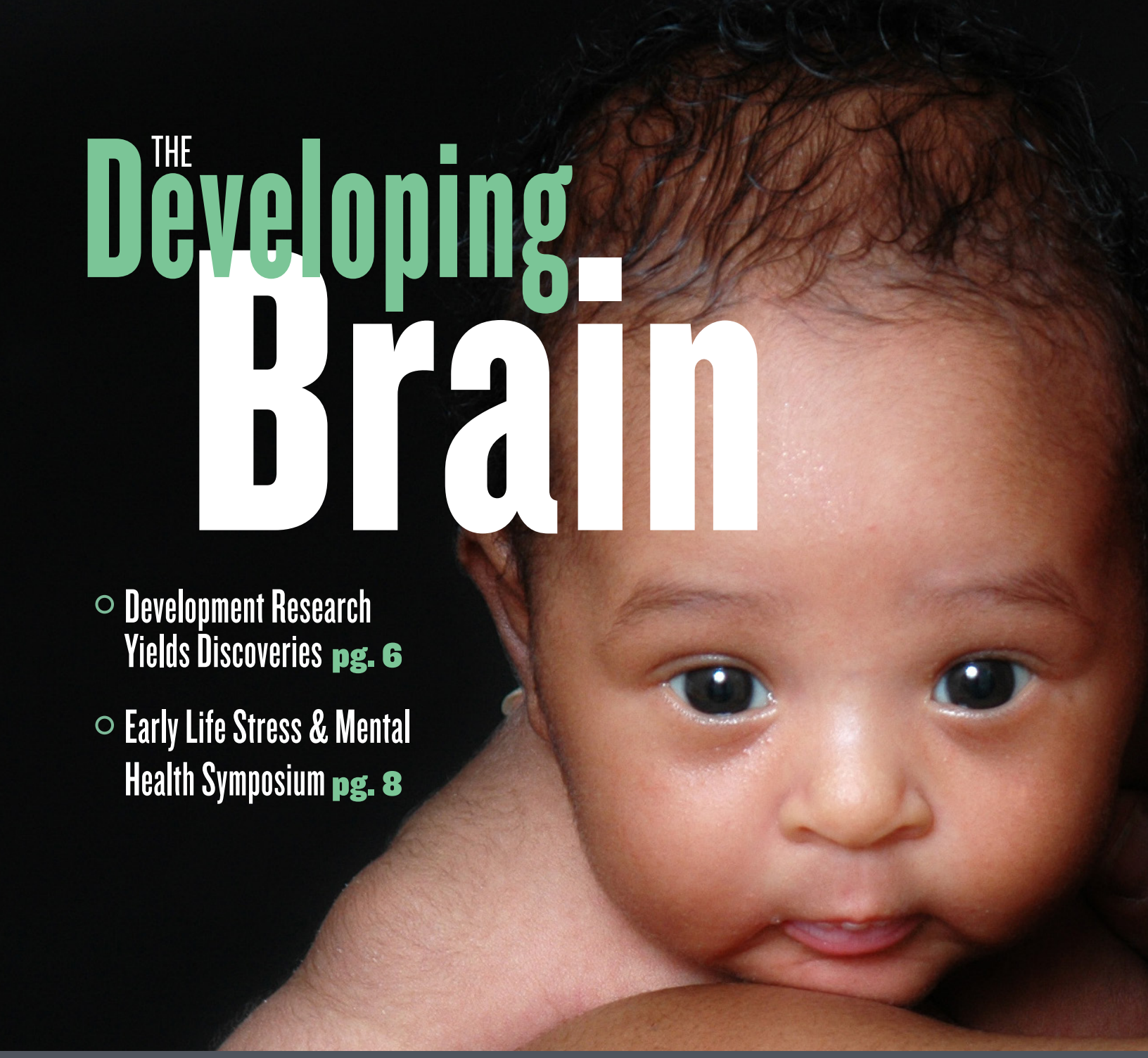

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MIT SUMMER 2018

THE PICOWER INSTITUTE FOR LEARNING AND MEMORY

DIRECTOR'S **MESSAGE**

Dear Friend,

If you've watched a baby grow up you've had the chance to be inspired by the brain. The transformation brought about by neural development, shaped by growth and plasticity and enriched by learning and memory, produces our amazingly capable minds. On page 5, Matt Wilson discusses the nature of intelligence and how the cognitive prowess that biology has evolved informs technology.

But the underlying mechanisms that make the brain develop into something so powerful are also intricate and delicate. Biological perturbations such as genetic or molecular abnormalities and environmental factors, such as early life stress or deprivation, can all too easily disturb or derail development. In this issue we report on a broad range of research, scholarship and experience related to the developing brain. We feature foundational research underway in our labs and the far-ranging and insightful discussion we convened with the JPB Foundation May 9 at our biennial spring symposium, "Early Life Stress & Mental Health."

I have long been interested by neural development. Indeed, it was the first area where I focused my research. In my lab's work, and in that of many of my fellow Picower Institute members, basic research has led to important findings with direct applicability to disease. You can learn more about brain development research around the Institute on page 6.

But not everything can be learned in the lab. Our symposium brought together a range of perspectives from physicians, educators, social workers and parents, as well as researchers, who shared what it takes to understand and fight toxic stress.

I am proud to be part of a community where we strive to discover and learn in so many different ways. You are part of this community, too. I hope you enjoy this latest chance to stay up to date on all of the developments.

LI-HUEI TSAI, DIRECTOR
Picower Institute for Learning and Memory

Circuit Helps Us Learn from Watching Others

SOME OPPORTUNITIES FOR LEARNING ARE better observed than experienced. Watching a neighbor frantically flee the new dog on the block, for instance, allows you to learn to beware without the stress of having that harrowing experience yourself.

Picower Institute scientist Kay Tye says this kind of learning, known as observational learning, offers a major evolutionary advantage.

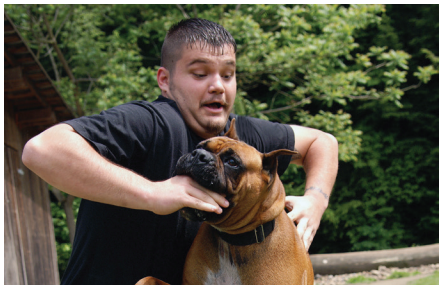
"So much of what we learn day-to-day is through observation," said Tye, associate professor of brain and cognitive sciences at MIT. "Especially for something that is going to potentially hurt or kill you, you could imagine that the cost of learning it first-hand is very high. The ability to learn it through observation is extremely adaptive, and gives a major advantage for survival."

In a new study published in *Cell*, Tye and her colleagues identified the brain circuit that is required for this kind of learning. This circuit, which is distinct from the brain network used to learn from firsthand experiences, relies on input from a part of the brain responsible for interpreting social cues. The researchers identified specific neurons in the anterior cingulate cortex that connect directly with neurons in the basolateral amygdala.

Former MD/PhD student Stephen Allsop, along with Romy Wichmann, Fergil Mills, and Anthony Burgos-Robles co-led the study in which they investigated what happens in the brains of mice as they observed another mouse receiving electric shocks paired with a cue such as a tone or light. When observer mice heard the cue one day later, they froze in fear, even though they had not experienced any shocks during the conditioning.

After the team located the specific circuit responsible, they blocked those connections during the observational learning task. When they did so, the observing mice did not learn to fear the cue.

In **Cell:**
Corticoamygdala Transfer of Socially Derived Information Gates Observational Learning, May 3, 2018, http://bit.ly/Obslearn



Protein Pair Quickly Makes Memories of New Places

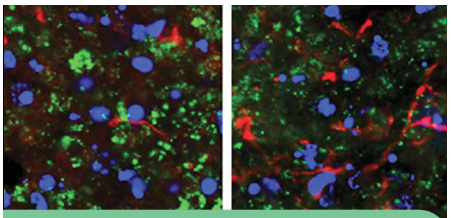
ENTERING AN UNFAMILIAR PLACE PROVIDES the chance to make a new memory. A new study at MIT's Picower Institute shows how two proteins spring into action to ensure that a memory is encoded within minutes.

While neuroscientists have known for a long time that new proteins have to be made for new memories to be formed, "We still had several layers of questions," said Weifeng Xu, assistant professor in the Department of Brain and Cognitive Sciences and senior author of the new paper in the *Proceedings of the National Academy of Sciences*. "How fast is protein synthesis required for memory encoding? What targets, or protein syntheses correlate with the encoding process? And are those targets required for the encoding?"

To find out, Xu's team, including lead author and Picower Institute research scientist Kendrick Jones, conducted experiments in mice in a memory-making region called the hippocampus. The proteins that they found to quickly team up, neurogranin and FMRP, are also present in humans and abmormal levels have been linked to mental health.

Xu's team tested the timeframe on which novel context memory occurs by using a drug to temporarily interrupt neural protein-making at different time points when introducing mice to a new space and then testing their memory later. Disrupting synthesis no longer prevented memory formation after a few minutes. In further experiments they identified neurogranin as a key protein, showed it was necessary, and showed that it is regulated by FMRP.

In **PNAS:**
Rapid, experience-dependent translation of neurogranin enables memory encoding, June 7, 2018, http://bit.ly/neurogranin



APOE4 cultures (left) have more amyloid (green) than APOE3 cultures (right).

How APOE4 Gene Increases Alzheimer's Risk

APOE4 IS THREE TIMES MORE COMMON among Alzheimer's patients than the general population but little is known about why this version of the APOE gene, which is normally involved in metabolism and transport of fatty molecules such as cholesterol, confers higher risk for Alzheimer's.

To shed light on this question, MIT neuroscientists performed a comprehensive study of APOE4 and the more common form, APOE3. Studying brain cells and organoids derived from a type of induced human stem cells, the researchers found that APOE4 promotes the accumulation of beta amyloid proteins.

"APOE4 influences every cell type that we studied, to facilitate the development of Alzheimer's pathology, especially amyloid accumulation," says Li-Huei Tsai, director of MIT's Picower Institute and the senior author of the study.

The researchers also found that they could eliminate the signs of Alzheimer's in brain cells and organoids with APOE4 by editing the gene to turn it into the APOE3 variant.

Picower Institute Research Scientist Yuan-Ta Lin and former postdoc Jinsoo Seo are the lead authors of the paper in *Neuron*.

Using the gene-editing system CRISPR/Cas9, the researchers converted APOE3 in stem cells derived from a healthy subject to APOE4. In neurons, the researchers found that cells expressing APOE3 and APOE4 differed in the expression of hundreds of genes — about 250 genes went down and 190 went up in cells with APOE4. In astrocytes and microglia the numbers were much higher.

These genetic changes also translated to differences in cell behavior that promoted higher amyloid beta accumulation in APOE4 models.

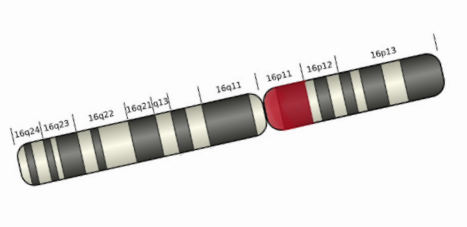
■ In **Neuron:**

APOE4 Causes Widespread Molecular and Cellular Alterations Associated with Alzheimer's Disease Phenotypes in Human iPSC-Derived Brain Cell Types. May 31 2018, http://bit.ly/ApoeTsai

Study IDs Gene Role in 16p11.2 Deletion Autism

PICOWER INSTITUTE NEUROSCIENTISTS studying of one of the most common genetic causes of autism identified a molecular mechanism that hinders how mice incorporate changes driven by experience. The findings in the *Journal of Neuroscience* suggest that the gene MVP is consequential in people with 16p11.2 deletion syndrome.

The 16p11.2 deletion occurs in people who are missing a small region of DNA near the center of one copy of chromosome 16. Scientists haven't known how the reduced presence of 29 protein-encoding genes, including MVP, leads to the disorder's symptoms.



"This has been a major problem for the field," said senior author Mriganka Sur, Newton Professor of Neuroscience and director of the Simons Center for the Social Brain at MIT.

MVP's specific function in neurons has barely been investigated. To change that, the researchers devised a series of tests of MVP in a well-understood region in the visual cortex, where the brain processes sight from both eyes.

Led by postdoctoral associate Jacque Pak Kan Ip, the team employed "monocular deprivation," or temporarily shutting one eye for a week. Normally, responses in visual cortex neurons related to the closed eye become weaker, but responses related to the remaining open eye become stronger. This neural circuit adjustment to experience is called "homeostatic plasticity."

In the normal mice, closing an eye for a week had the expected effect. But in mice with one copy of MVP missing, the researchers observed a telling difference. Responses related to the closed eye still weakened, but responses from the open eye did not get stronger. Homeostatic plasticity was disrupted.

■ In **J. Neurosci:**

Major vault protein, a candidate gene in 16p11.2 microdeletion syndrome, is required for the homeostatic regulation of visual cortical plasticity, Mar. 14, 2018, http://bit.ly/MVPautism

Working Memory 'Sync' Sinks with Heavy Load

A NEW PICOWER INSTITUTE STUDY FINDS that the "coupling," or synchrony, of brain waves among three key regions breaks down when visual working memory load becomes too much to handle.

"When you reach capacity there is a loss of feedback coupling," said senior author Earl Miller, Picower Professor of Neuroscience. That loss of synchrony means the regions can no longer communicate with each other to sustain working memory.

Understanding what causes working memory to have an intrinsic limit is important because it could help explain the limited nature of conscious thought and optimal cognitive performance, Miller said. Working memory capacity is correlated with intelligence.

And because certain psychiatric disorders can lower capacity, said Miller and lead author Dimitris Pinotsis, a research affiliate in Miller's lab, the findings could also explain more about how disorders, such as schizophrenia, interfere with thinking.

The new study in *Cerebral Cortex* is an analysis of data recorded when animal subjects played a game that sometimes exceeded their working memory capacity. The researchers measured brain waves in three regions: the prefrontal cortex (PFC), the frontal eye fields, and the lateral intraparietal area. The regions essentially work as a committee to keep working memory going but that changes as load approaches and then exceeds capacity.

"At peak memory load, the brain signals that maintain memories and guide actions based on these memories reach their maximum," Pinotsis said. "Above this peak, the same signals break down."

In particular, above capacity the PFC's coupling to other regions at low frequency stopped, Miller said.

■ In **Cerebral Cortex:**

Working Memory Load Modulates Neuronal Coupling, March 28, 2018, http://bit.ly/memorysynch

Fellowships Develop the Next Generation of Research Leaders

A DOCTORAL DEGREE IS A MAJOR MILESTONE, but it's not the end of the scientific training road. Scientists learn to run their own research program in followup postdoctoral training experiences.

With a new, competitive program, created with the JPB Foundation, the institute now offers 14 "Picower Fellows" – one per faculty lab – the space, resources and support needed to run their own programs and pursue an independent research agenda, freed from the burden and uncertainty of trying to secure fellowship funding. The program provides career development training, mentoring and regular networking opportunities to help place them in positions and fields where they can flourish. The program held its first symposium of fellows' research June 14.

Since 2011, the Institute has also offered the Picower Clinical Fellowship Program, in which a young physician joins a Picower Lab. Dr. Michael Halassa, a new assistant professor of Brain and Cognitive Sciences at MIT was a clinical fellow in the lab of Matt Wilson. Now Dr. Ravi Raju holds the fellowship in the lab of Li-Huei Tsai. To Raju, who studies the biological impact of early life stress, the chance to work in the lab is about integrating neuroscience research and medical practice to help children thrive. The institute hopes to expand the program to support more fellows.

"I'm incredibly passionate about dismantling the silos that currently exist between basic science, public health and clinical medicine," Raju said. "If we really want to move the needle on social disparities, we need to find innovative ways to tackle the problem. And that will require disciplines coming together that haven't traditionally been at the same table."

Picower Fellows get career advice from Picower alumnus Jeff Gavornik, now at Boston University.

O, Canada!

When Canadian Prime Minister Justin Trudeau visited MIT May 18, Professor Li-Huei Tsai (center) was invited to present her research. With lab member Dr. Diane Chan (left) and MIT VP for Research Maria Zuber (right), Tsai told Trudeau about how non-invasively instilling gamma waves in the brain is showing early, experimental promise against Alzheimer's disease. Chan reports Trudeau asked several insightful questions about the nature of gamma rhythms and how they can be affected.

Credit: Adam Scotti

Symposium Speaks to the Many Powers of Brain Rhythms

A STANDING-ROOM-ONLY AUDIENCE AT THE Picower Institute April 4 learned the power of brainwaves: They endow us with some of our most prized cognitive abilities, and when they falter, they leave us with some of our most difficult and tragic diseases.

Sponsored by the Aging Brain Initiative, an MIT-wide collaboration to understand how aging puts our brains at risk for neurodegeneration, "Brain Rhythms in Health and Disease" featured deep discussions of how neural oscillations coordinate functions such as computation, cognition, and learning and memory, but also play roles in Alzheimer's disease (AD) and schizophrenia. Wolf Singer of the Ernst Strüngmann Institute gave the keynote.

Picower Professor Earl Miller described a new model of working memory in which beta waves control gamma rhythms to give us the freedom to control what we hold in mind. Annabelle Singer, a former MIT postdoc and now an assistant professor at Georgia Tech, described the latest findings in her collaboration with Picower Professor and Institute Director Li-Huei Tsai showing how non-invasively entraining gamma rhythms in the brain produces profound benefits in AD mice. For full coverage visit http://bit.ly/wavesymp.

Earl Miller presents "Working Memory 2.0" at "Brain Rhythms in Health and Disease." Credit: Adrianne Mathiowetz.

Q&A with Matt Wilson: Intelligence research at MIT

MIT recently announced the "Intelligence Quest." President Rafael Reif said the campuswide initiative will pursue two key questions: "How does human intelligence work, in engineering terms? And how can we use that deep grasp of human intelligence to build wiser and more useful machines, to the benefit of society?"

As associate director of the Center for Brains Minds and Machines (CBMM), Matt Wilson, Sherman Fairchild Professor in Neurobiology, helps lead such research. He answered questions about the initiative, intelligence research and the nature of intelligence itself.

What is MIT IQ?

MIT IQ seeks to develop and apply artificial intelligence (AI) and machine learning to broad disciplines within the engineering and science communities. The question is how can we use AI to advance science and how can science help us to advance fundamental approaches in AI? CBMM, funded by the NSF, grew out of an earlier MIT initiative called the Intelligence Initiative. It was developed to drive the study of intelligence, not just AI, but trying to understand biological intelligence, and from that, gain insights into how the understanding of real intelligence might advance AI.

The expectation is that effort will continue and help to drive a significant part of MIT IQ in its objective of determining how we can bring together the community, and how can we invest and develop resources that can increase the penetration of machine learning and AI throughout MIT.

What is real intelligence?

Neuroscience studies the only real example of intelligence: biological intelligence. The one true test of intelligence is the ability to survive and adapt in the real world. Dealing with complexity and uncertainty and developing behavioral strategies that allow you to succeed under those conditions is what we think of as genuine intelligence.

How does biological intelligence inform AI?

That's the big question. There have been many successes of machine learning and AI algorithms, for instance in visual object recognition. That involves sophisticated pattern recognition in which you train networks on large datasets to develop representations that are capable of doing very effective and efficient detection, recognition, classification, and labeling. Many of those approaches – these deep layered networks – have been inspired by the kind of multiple layered networks found in the visual system.

Newer applications of AI require more flexible synthesis: multiple sources of information, and general inference based on limited information. The application to self-driving cars is a good example. It's not just recognizing the scene, it is knowing what is going to happen next given your understanding or models of entities or agents that are present. That is the reason intelligent biological agents are successful in the world. They are capable of building internal models of the world and using these models to make predictions, to establish expectations and to deal with uncertainty. The future of AI is one in which we understand how biological-like networks generate and apply internal models of the world.

General intelligence, which is a good description of biological intelligence, is one network that essentially solves all the problems as opposed to many networks that solve very narrow sets of problems. The current generation of AI algorithms tend to be very domain specific. Solving the Artificial General Intelligence problem and taking the kinds of insights that have been gained from biology in doing so would be a broad mission of CBMM and the core mission of the MIT IQ initiative.

How might these efforts intersect with Picower?

The natural evolution of this work is through broader collaborations between neuroscience and those working in computational neuroscience and computer science: thinking about problems from a synthetic perspective and building artificial networks capable of reproducing the properties seen in biological networks. Those kinds of collaborations are going on right now. We have people working on biological systems that are using sophisticated tools for measuring and manipulating large scale networks, and then trying to interpret that data based upon synthetic networks that are generated and evaluated with the help of computational neuroscientists and computer scientists.

What do you hope the impact of this work will be?

The promise of AI is developing tools that will allow us to solve problems that we had considered previously inaccessible, for instance, by bringing together vast sources of information which can be for any individual person very difficult to understand. Artificial algorithms will have the capacity to digest and discover solutions to problems that we might have missed. Solving the problem of AI is in a sense solving all of the other problems that we might have.

DEVELOPMENT RESEARCH YIELDS

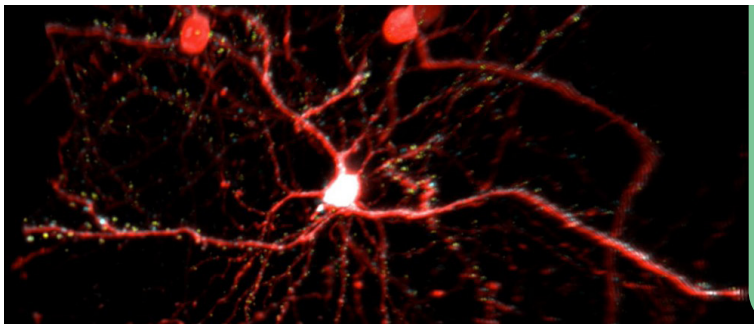
Discoveries, Insights, & Innovations

Developing minds are naturally curious, and many Picower Institute scientists are naturally curious about developing brains. Their long-term research has yielded important discoveries, and along the way, new strategies to improve mental health and novel technologies.

"We have spent many decades trying to understand how experience and deprivation modify the development of the cortex and are at a point where we think we've learned enough to take advantage of that understanding to develop novel strategies to overcome developmental disabilities," said Picower Professor Mark Bear.

Bear was speaking about his lab, but in a more general way, he could also be speaking about several Picower colleagues. With different journeys into studies of neurodevelopment, they have all advanced science and, as a result, potentially, health and technology as well.

> "We have spent many decades trying to understand how experience and deprivation modify the development of the cortex and are at a point where we think we've learned enough to take advantage of that understanding to develop novel strategies to overcome developmental disabilities."
>
> **Mark Bear**



Multi-color two photon imaging of neurons, co-developed by the Nedivi lab, shows different kinds of synapses in vivo.

Insightful genetics, innovative microscopy

Professor Elly Nedivi's lab, which started at MIT in 1998, has discovered genes underlying plasticity – the capability of the central nervous system to remodel its circuits in response to experience and activity. Plasticity is always happening, Nedivi said, but it is most prominent during development. Many capabilities such as language, vision, or even socialization can only fully develop within a "critical period" of youth when brain circuitry is molded by the environment.

In plasticity, the connections between neurons, or synapses, get stronger or weaker. Nedivi wanted to know how. She set out to find "candidate plasticity genes." Nedivi's screens led to hundreds of genes that are responsive to neural activity, but she honed in on ones whose proteins are expressed specifically at the synapse, in response to natural environmental stimuli, and that associate with cellular remodeling. She's focused on two that had not been studied before: CPG2 and CPG15.

"We've basically followed them where they took us," Nedivi said.

She's shown that CPG15 encodes an extracellular signaling molecule that promotes synapse stability and neural growth. CPG2 expression regulates receptors at the synapses of glutamate-producing neurons. CPG2 also happens to be the product of a gene that is number two on the list of those most strongly associated with risk for bipolar disorder. Nedivi didn't set out to study bipolar disorder, but this is an example of how curiosity about fundamental aspects of development can lead to discoveries relevant to human health. Now her lab is working to understand the functional significance of human mutations in the gene and their relation to bipolar disorder.

Nedivi's studies have also contributed to understanding plasticity in adults. Synapses are constantly remodeling, but while it's not hard to see dramatic synaptic changes during development, changes are more subtle in the adult brain. Nedivi's desire to observe synapse remodeling in the context of the living brain, has compelled her to develop new tools. In collaboration with MIT mechanical engineer and optics expert Peter So, Nedivi has devised ways to image whole neurons at synaptic resolution, and to add new colors to two-photon imaging to allow simultaneous and distinct imaging of inhibitory and excitatory synapses in real time in live mice. More recently they have devised a way to make imaging faster so that more ephemeral phenomena do not go unnoticed.

From ferrets to clinical trials

Newton Professor Mriganka Sur has spent more than 30 years at MIT studying the basic rules of plasticity. Soon after he arrived, he made a particularly powerful demonstration. In developing ferrets, Sur and his colleagues

disconnected the hearing pathways to auditory centers, including the auditory cortex. Astonishingly the ferrets did not leave that cortex fallow for lack of stimulation. Instead they innervated the auditory cortex with inputs from the eyes, creating a supplementary visual cortex, and repurposing unused neural resources to go where the sensory action was. 'Rewired' ferrets could use their auditory cortex to see.

Since then, he's continued to study the rules and mechanisms of plasticity. His lab discovered hundreds of genes and microRNAs used by the visual cortex to change synapses. All synapses change in response to experience: some, driven by specific molecules, strengthen, whereas others, driven by different molecules, weaken. Together, these changes rewire circuits but keep overall activity levels similar.

In one line of research, his lab discovered in 2009 that expression of MeCP2 changes considerably amid plasticity, participating in a synapse-enhancing pathway with a protein called IGF1. Lacking MeCP2 is a cause of the neurodevelopmental disorder Rett Syndrome. Sur's lab found that mice lacking MeCP2 had increased plasticity in visual cortex. When they gave MeCP2 knock-out mice injections of IGF1, they restored plasticity to normal levels, opening up a therapeutic possibility for Rett. Now the approach is being tested in clinical trials.

This spring Sur's lab also published research showing that a different form of plasticity in the visual cortex depends on a pathway involving the gene MVP, which is one of the genes lost in 16p11.2 deletion autism (See page 3).

Theory begets strategy

Inspired by Hubel and Wiesel's 1963 demonstration that a kitten temporarily deprived of vision in an eye during a critical period lost vision in that eye forever, Bear set out to understand plasticity in vision and learning and memory.

At Brown University in the 1980s and '90s he collaborated with physicist Leon Cooper, who had co-developed a mathematical theory of plasticity. An important prediction was that sometimes active neural connections called synapses should weaken, a process called long-term depression. Bear's lab showed LTD was real.

"We found a protocol that elicited LTD," Bear said. "That got the whole ball rolling on LTD and now there are 1,000s of papers."

LTD is enormously consequential in development, Bear said. Young brains form way too many synapses and then edit, or "prune" them away with maturity. One scientist has even calculated that the developing monkey visual cortex loses 5,000 synapses per second during adolescence, Bear said.

In the hippocampus, Bear showed that one form of LTD requires rapid protein synthesis at the synapse. The finding led to a focus on a protein called FMRP, which stands for Fragile X mental retardation protein because its loss causes the intellectual disability disorder Fragile X syndrome.

Bear joined Picower in 2003. His research here showed that FMRP acted as a brake on LTD by regulating protein synthesis. In 2007 his lab showed they could ameliorate Fragile X in mice by inhibiting the receptor that stimulates protein synthesis and triggers LTD, called a metabotropic glutamate receptor. Bear subsequently formed a company to test the strategy in clinical trials.

All along, Bear lab's retained its interest in vision. In 2016, years of research on visual plasticity resulted in a radical idea for treating amblyopia, a common form of monocular vision loss in children. In animals they found that temporarily disabling both eyes with a blowfish toxin essentially "reboots" plasticity in both eyes, allowing the eye with lost vision to rebuild sight, another potential therapy born from underlying theory.

Discovery and diversity

Neural development helped to launch Picower Professor Li-Huei Tsai's career in brain science, though she didn't necessarily expect that. As a cancer researcher at Harvard in the early '90s Tsai identified a particular enzyme, Cdk5, that turned out to only be active in the nervous system.

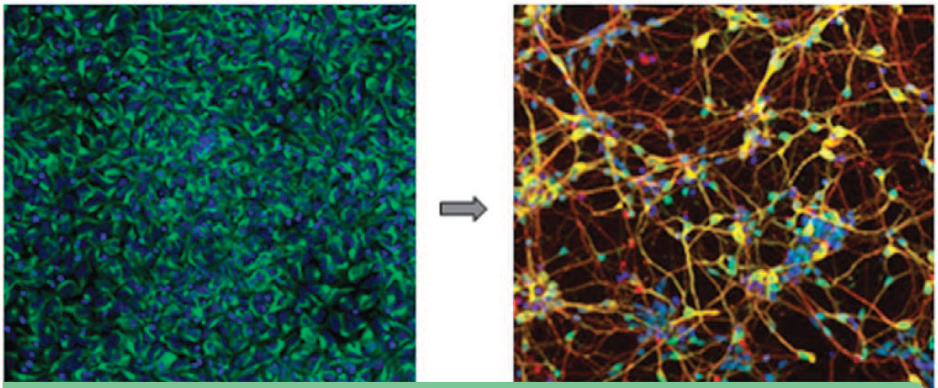
Tsai's studies of Cdk5 revealed that it was crucial for neural development, in particular the migration of newly born neurons to the cortex. Without Cdk5, the brain wouldn't form its characteristic lamination, leading to abnormal neural circuit formation and epileptic activity.

In later work, Tsai discovered that when a protein called p35 that regulates Cdk5 breaks down into p25, the ensuing overactivity of Cdk5 leads to neurodegeneration in the adult brain, a crucial insight into Alzheimer's disease. Her lab invented a powerful model of Alzheimer's, the p25 mouse, to inform research.

Tsai, who arrived at MIT in 2006, still studies development in diverse ways. In one program, her lab is investigating Down syndrome by using induced stem cells from patients to grow new "minibrain" organoids. In the lab, her team can watch how the model brains develop differently from ones without the chromosomal abnormality.

Tsai's lab also houses the work of Picower Clinical Research Fellow Dr. Ravi Raju, who spoke at the May 9 symposium. He is asking how modeling poverty-like early life stress in mice may cause gene expression to differ. He has found that mice who make specific "epigenetic" changes are better able to resist anxiety than mice who don't.

Development is a process, and often one never knows exactly how it will turn out. The same could be said for studies of brain development.



A Sur lab study of the MECP2 gene captured images of neural progenitor cells and, later, newborn neurons.

FIGHTING TOXIC STRESS TOUGH BUT POSSIBLE

Symposium Speakers Say

Dr. Ravi Raju describes his research showing that the resilience of mice reared in a model of poverty is associated with measurable patterns of gene expression. Credit: Adrianne Mathiowetz

Through compelling personal stories and dramatic research evidence, speakers at the Picower Institute for Learning and Memory's May 9 symposium "Early Life Stress & Mental Health" showed that with science and activism people are making progress in helping children survive toxic stress.

Whether in the lab, the clinic, or the community, the key is to ask deep questions and to invest the time and energy to grapple with the heartbreaking, multifaceted complexity underlying how adverse experiences such as neglect or abuse can affect the health of children. It can lead to strikingly higher likelihoods of mental illness and reduced lifespan.

"We do everything that we can to help primarily low-income children and parents," said Barbara Picower, president of the JPB Foundation, which supports many of the event's speakers and collaborated with the Institute to organize the daylong conference, a biennial event at MIT since 2012. "Toxic stress is something that is so damaging to children, the results of it occur through the lifetime."

Added MIT Provost Martin Schmidt, "The topic of this symposium could not be more important for our society, morally or practically."

Speakers reinforced Picower and Schmidt's introduction with an abundance of data. New Jersey children traumatized by Superstorm Sandy in 2012, even if their homes suffered only "minor" damage, were 5 times more likely to be depressed and to report feelings of nervousness and fear years later, reported Patricia Findley, associate professor of social work at Rutgers University.

> "If you aren't willing to take the time to actually figure out what's happened to a child you might treat the child for something that isn't really causing that kid to be sick. You have to really take the time to understand."
>
> **Geoffrey Canada**

And Dr. Nadine Burke Harris, a pediatrician and founder of the Center for Youth Wellness in San Francisco, presented data from a major review study and other sources showing that experiencing four or more adverse childhood events (ACEs) is associated with an 5.6-fold risk of drug abuse, an 11-times increased risk of

Alzheimer's and a 30-times greater risk of suicide. In all, ACEs can reduce longevity by decades.

Dig deeper

Though such associations are well known, Burke Harris said, few pediatricians screen for ACEs. But failing to discover those underlying problems can lead to misguided treatment.

Many behavioral problems associated with toxic stress, for example, come across as ADHD but are caused by the chronically elevated inflammatory, or "fight-or-flight" response that stressed children live with, she said. The response originally evolved for surviving dangers like encountering a bear in the forest. "The problem is what happens when that bear comes home every night," she said.

Without screening for that underlying stress, doctors often prescribe ritalin, a stimulant. But in a child enduring a chronic stress response that medication likely won't do much good. Instead, if screening reveals ACEs, Burke Harris works to mitigate the stresses and prescribes guanfacine, which calms the nervous system and reduces blood pressure.

Keynote speaker Geoffrey Canada, president of the Harlem Children's Zone, told a similar anecdote about the need to dig deeper. Years ago, a social worker in HCZ's after-school program alerted him to a child who began to display bizarre behaviors such as talking to himself. Rather than just sending the child to a doctor, Canada sent the social worker to visit the home. The visit revealed that the tiny apartment was infested with rats and the child's mother, who needed to work, had tasked the boy with guarding his younger sisters from being bitten at night. The boy's problem was not mental illness so much as a profound lack of sleep.

"If you aren't willing to take the time to actually figure out what's happened to a child you might treat the child for something that isn't really causing that kid to be sick," Canada said. "You have to really take the time to understand."

The desire to dig deeper brought Dr. Ravi Raju to the lab of Picower Institute Director Li-Huei Tsai, where he is a Picower Clinical Fellow. After observing stark health and income disparities among Boston children during his pediatrics residency at local hospitals, Raju decided to do fundamental research on how deprivation amid poverty affects the brain. Using an experimental protocol in which mice are deprived of nesting materials, an important component of pup rearing, Raju has shown that baby mice appear to adapt via specific changes in gene expression. Those that do remain resilient. Those that don't become very anxious. Studying those genes and the molecular pathways they affect when expressed is revealing potential therapeutic targets for mitigating toxic stress, he said.

In India, MIT economics professor Frank Schilbach is testing interventions to help alleviate poverty cycles. His research shows how intricately problems in households are intertwined. Among poor workers, for instance, back-breaking labor leads to debilitating pain. With poor healthcare, many laborers start drinking to feel better. Difficulties at home, including for their children, often follow. Amid this cycle, he's found, is poor sleep, an often underappreciated factor where interventions could help.

Babies show amazing acumen in what they pick up from the adults around them, said MIT cognitive scientist Laura Schulz, professor in the Department of Brain and Cognitive Sciences. She described her research demonstrating that babies will match the degree of effort they observe a grown-up making when trying to figure a task out. Another set of experiments shows how adults can constrain a child's thinking. If an adult specifically demonstrates only one feature of a multi-featured toy, for example, a child won't explore the toy to discover any of its other features.

Speaking up

As important as speakers said it is for scientists, physicians and social workers to engage in deep, energetic efforts to understand the underlying cognitive abilities and vulnerabilities of children, several other speakers emphasized how crucial it is for afflicted communities and people to insist on being heard.

Dr. Mona Hanna-Attisha, associate professor of pediatrics at Michigan State University, spoke at the symposium about the extensive research she did to prove the horrible extent of lead poisoning among children in Flint, Mich., after the city infamously switched its water supply a few years ago. Community complaints about foul water were dismissed. Research documented how wrong that was.

"They were told the water was fine," she said. "Science is not meant to live in publications and journals and ivory towers. The purpose of science is to benefit our communities."

After she revealed the problem, social and health services have increased in the city, but now the fight continues to sustain funding for those restorative efforts, said Hanna-Attisha, who won an MIT Media Lab "Disobedience Award."

Though pollution is an abundant problem, other speakers described how the environment can protect against toxic stress. Marc Berman, assistant professor of psychology at the University of Chicago, described his findings

JPB Foundation President Barbara Picower delivers opening remarks at the May 9 symposium, "Early Life Stress & Mental Health." Credit: Adrianne Mathiowetz

that exposure to trees and natural scenes may improve cognition. Meanwhile Jonathan F.P. Rose, a prominent builder of progressive mixed-income communities, described how his developments incorporate vegetation, as well as medical and social services rather than just providing housing.

But several speakers made it clear that they've had to advocate and sometimes fight systems to mitigate toxic stress in their communities. On a panel with Frank Farrow of the Center for the Study of Social Policy and Boston University pediatrician Renee Boynton-Jarrett, local parents Lisa Melara and Gihan Suliman spoke of their tireless volunteer work to help parents find supportive community resources and understand their rights. Later in the day, journalist and filmmaker Jose Antonio Vargas, CEO of Define American, described his work in creating communities among undocumented immigrants such as himself, to help fight hatred by ensuring their stories are told.

Several speakers pulled no punches about how ongoing problems of poverty, violence, substance abuse and racism continue to produce toxic stress in children, even as they also reported their strides in research and community action to mitigate its effects.

Harvard University Professor and child health expert Jack Shonkoff noted that for all the advances in research and community services, their impact has not been nearly enough. He put it all in terms of the "Stockdale Paradox," named for a former U.S. prisoner of war in Vietnam. To survive, one must never lose hope of ultimately prevailing, goes the paradox, even while remaining brutally honest about how dire the current situation really is.

The IMPACT of *Giving*

Belfers combat Alzheimer's disease with support for Aging Brain Initiative

ROBERT AND RENEE BELFER HAVE LONG supported MIT's research programs in neurodegenerative diseases, such as Alzheimer's disease.

Alzheimer's disease affects 5.2 million Americans and costs the country about $250 billion a year. As the population ages, the cost of caring for people affected by Alzheimer's may exceed $1 trillion a year by 2050.

The Belfers said they view Alzheimer's as a national security threat. They have renewed their commitment to ameliorating it with an additional gift to MIT's Aging Brain Initiative and research by Professors Li-Huei Tsai, Emery Brown and Ed Boyden.

From Petroleum to Philanthropy

Bob Belfer immigrated to America at age seven in 1942, growing up in Brooklyn, New York with his "beloved Dodgers." Belfer graduated from Columbia College in 1955 and the Harvard Law School in 1958. Renee and Bob married in 1960, and he began his career with Belco Petroleum Corp., a Fortune 500 company where he was president for 20 years.

Now Belfer says it is philanthropy that predominately occupies his time.

"Our vibrant economic system greatly rewards successful entrepreneurs and these entrepreneurs should recognize their good fortune and bring their organization's talents, as well as their financial support, to serve the common good," he said. Five years ago, Bob and Renee's foundation did just that.

In 2012, the Robert A. and Renee E. Belfer Family Foundation created the Neurodegeneration Consortium (NDC) to advance the study and treatment of Alzheimer's and other neurodegenerative diseases. The NDC is a unique multi-institutional initiative based at the University of Texas MD Anderson Cancer Center that also encompasses the Picower Institute, Baylor College of Medicine, and Mount Sinai Hospital in New York.

"The aim is to translate research findings into effective targeted drugs and diagnostics for patients while addressing quality-of-life issues and the financial challenges of treating and living with Alzheimer's and other aging diseases," said Belfer. The NDC has already borne fruit in the development of new therapeutic approaches.

Supporting Gamma Rhythm Research

Last year, with funding from the Belfer Family Foundation, Tsai's lab published research demonstrating that they could reverse memory loss in mice by interfering with an enzyme, HDAC2, that forms a genetic blockade that causes cognitive decline.

Pharmaceutical companies had tried to develop treatments to block HDAC2 with limited success and many toxic side effects. Tsai's Picower Institute team developed the method to precisely target HDAC2 using a large protein fragment to interfere with the enzymatic function.

But it was another program — restoring gamma brain waves and cognitive function — that motivated the Belfers' latest giving.

By using light flashing at the gamma frequency of 40 Hz, Tsai, Brown and Boyden have shown that cellular function can be restored in mouse models to help reduce and remove amyloid plaques associated with Alzheimer's disease and at least temporarily reverse cognitive decline.

The Belfers said they were excited by the breakthrough.

"Because of its noninvasive nature, this approach has great potential for an early breakthrough in Alzheimer's therapy following years of failure by expensive efforts on the part of big pharma," Bob Belfer said.

Tsai said the Belfers' gift will help the Aging Brain Initiative-affiliated trio to continue this promising research, including advancing understanding of how it may work in human patients.

"Testing a new therapy is a complicated and expensive process," Tsai said. "Bob and Renee's support will play an essential role in allowing us to continue to understand how gamma therapy produces its benefits and how it might be properly implemented in clinical applications."

Strengthening Basic Science Research

The Belfers said they recognize that pharmaceutical companies motivated by immediate profits and government agencies tentative about funding long-term research projects can't effectively bridge the gap in research from bench to bedside for neurodegenerative diseases.

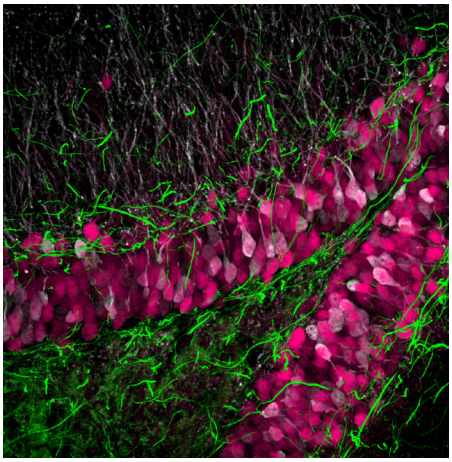
"Public demands for government services overwhelms the monies raised by current taxes," Bob Belfer said. "The aging of the population exacerbates this as people live longer and become more likely to develop the diseases of aging."

The Belfers said they are privileged to be able to support MIT as a unique place to foster scientific discoveries and enhancements across wide and diverse areas of science, especially in diseases of aging.

"An aging population challenges us with runaway medical costs," Bob Belfer said. To enhance the quality of life in later years, as well as reduce costs, we need a national effort. "Efforts such as the NDC and MIT's Aging Brain Initiative," he added, "are needed to address this 'urgent national problem'."

Upcoming EVENTS

For the *latest* information on all our lectures, symposia and other events, please visit: **picower.mit.edu/events**



SYMPOSIUM

10.23.2018 *Frontiers in Neurotechnology*

The Picower Institute's Fall Symposium, organized by Assistant Professor Kwanghun Chung, will bring together experts who are working at the leading edge of the development of neurotechnology.

Paola Arlotta, PhD, is a professor at Harvard University. Her work includes generating next-generation, long-term cultures of 3D cerebral organoids, starting from human induced pluripotent stem cells, as part of an overall research agenda of studying programming, reprogramming and modeling of the mammalian cerebral cortex.

Emery Brown, PhD, MD, the Edward Hood Taplin Professor at MIT and a member of the Picower Institute, is an anesthesiologist-statistician whose research has made important contributions to understanding how anesthetics act in the brain and has developed signal processing algorithms to solve important data analysis challenges in neuroscience.

Kwanghun Chung, **PhD,** is a member of the Picower Institute, assistant professor in MIT's Department of Chemical Engineering and Institute for Medical Engineering and Science. He has invented several tissue transformation and processing techniques that vastly improve the data available through neuroimaging including CLARITY, SWITCH, stochastic electrotransport, MAP, and SHIELD.

Elizabeth Hillman, PhD, is a professor of biomedical engineering at Columbia University. A major theme of her lab is *in vivo* neuroimaging, for instance to study blood flow and neuronal activity, leading to the development of advanced technologies including laminar optical tomography and hyperspectral two-photon microscopy.

Na Ji, **PhD,** associate professor of molecular and cell biology and of physics at UC Berkeley, develops and applies novel imaging methods to understand the brain. Ji also aims to extend the applications of her lab's technologies to other living (and nonliving) systems.

David Kleinfeld, PhD, holds the Dr. George Feher Experimental Biophysics Endowed Chair at UC San Diego. His lab employs a wide variety of techniques for studies of phenomena including sensory behaviors, microcirculation in the brain, neuromodulation, and learning.

Ed Lein, PhD, is an investigator at the Allen Institute for Brain Science providing scientific guidance and oversight for the creation of large-scale gene expression atlases of the mammalian brain, including the human brain, as online resources for the scientific community.

Sergiu Pasca, MD, is an assistant professor of psychiatry and behavioral sciences at Stanford University. His lab studies brain development and dysfunction. Techniques include 3D "brain in a dish" tissue cultures and other state-of-the-art stem cell biology, genome engineering, live imaging and neurobiology approaches.

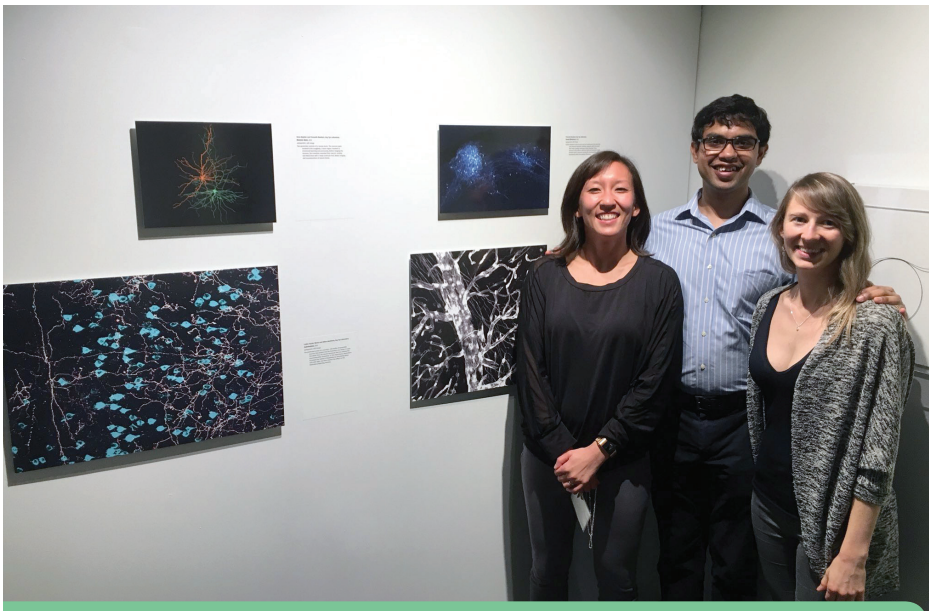
Orly Reiner, PhD, is a professor in the Department of Molecular Genetics at the Weizmann Institute of Science where she studies embryonic brain development and disease using approaches combining molecular, biochemical, *in vivo*, *ex vivo*, and *in vitro* studies with mouse and human brain organoid models.

EXHIBIT

The Beautiful Brain: Now – Dec. 31

Spanish neuroscience pioneer Santiago Ramón y Cajal made transformative discoveries of neural anatomy. "The Beautiful Brain: The Drawings of Santiago Ramón y Cajal," which opened last month at the MIT Museum, includes approximately 80 of his drawings.

Cajal's historical works are complemented with contemporary neuroscience images by scientists from MIT (including Picower faculty members Susumu Tonegawa and Kay Tye) and around the world. Many of them were created using technologies pioneered here at MIT as well. This traveling exhibition, supported by the Picower Institute, is organized by the Frederick R. Weisman Art Museum and the Cajal Institute in Madrid. It runs through December 31, 2018, so stop by if you can.



Kay Tye (left) attends the exhibit with lab members Praneeth Namburi and Gillian Matthews.

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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, and consciousness. Institute researchers explore the brain 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: 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; **Li-Huei Tsai**, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Director, The Picower Institute for Learning and Memory; **Kay Tye**, Associate 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.