



# The Brain and the Body

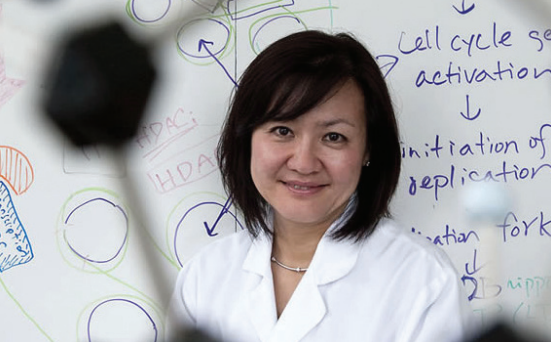
pg. 8

**ALSO INSIDE** 2-4 Alzheimer's, Epilepsy Research News 4 Graduate Women of Excellence  
6 Impact of Giving 7 New Fund for Cannabis Research 10 New Art Installation

## Neuroscience News

**MIT** SUMMER 2019

 **THE PICOWER  
INSTITUTE**  
FOR LEARNING AND MEMORY



## DIRECTOR'S MESSAGE

Dear Friends,

As neuroscientists, we have learned that one of the most crucial properties of a productive mind is openness – being open to new ideas and possibilities. This, of course, is apparent in many fields, but this issue of *Neuroscience News* just happens to contain a series of recent examples of how taking less traveled roads and embracing surprises has resulted in some fascinating and important new advances.

Our cover story (see p. 8) discusses how three of our faculty members – Emery Brown, Gloria Choi and Steve Flavell – are helping to show that studying the brain sometimes requires studying other parts of the body, like the immune system, the digestive tract, the circulatory system, or even the “microbiome” – the colonies of other organisms that live in our bodies with us. That’s not traditional brain science, but it makes a big difference. Emery says studying the body’s damage-sensing, or “nociceptive,” system has changed the way he practices anesthesiology. Gloria has uncovered the mechanism by which maternal illness can result in autism-like symptoms in offspring, and Steve has shown a critical link between the microbiome and the brain.

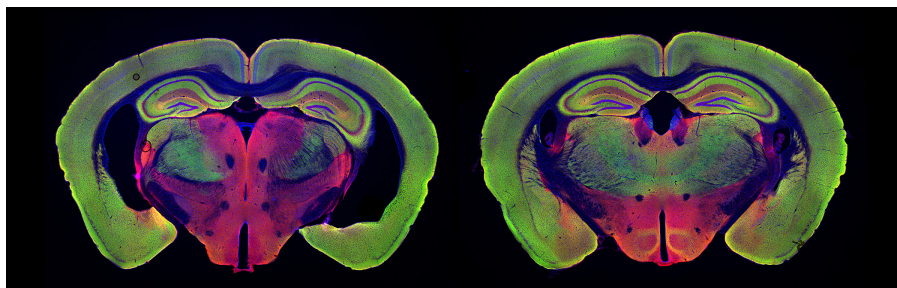
Openness to new and surprising ideas has made a difference in my lab, too. It has been unexpected and amazing to see the huge differences sensory stimulation of brain rhythms makes in Alzheimer’s model mice (see this page). We are hopeful, as testing begins, that we’ll see the same results in people.

In science, open inquiry requires open minded supporters. In this issue we report on two such MIT alumni: Lester Gimpelson (p. 6) who has supported my lab’s work and Charles Broderick (p. 7), who is funding new research in Earl Miller and Myriam Heiman’s labs on cannabis, a substance long shrouded in taboo and therefore mystery about how it actually affects brain development and behavior.

We’re glad you’ve opened this issue and we hope you enjoy exploring the ideas inside.

**LI-HUEI TSAI, DIRECTOR**

*Picower Institute for Learning and Memory*



Large ventricles (openings) are apparent in the untreated Alzheimer’s mouse brain on the left. There is much less neuron loss in the brain on the right, which was treated with sensory stimulation.

## Visual Stimulation of Gamma Rhythms Shows Benefits in Alzheimer’s Model Mice

**Picower Institute researchers have found** that exposing multiple mouse models of Alzheimer’s disease (AD) to light flickering at the 40 Hz frequency of a gamma rhythm in the brain has widespread benefits, including reduced inflammation, enhanced synaptic function, and protection against neuron death.

“It seems that neurodegeneration is largely prevented,” said Picower Professor Li-Huei Tsai, director of the Picower Institute for Learning and Memory and the senior author of the study published May 7 in *Neuron*.

The team led by postdoc Chinnakkaruppan Adaikkan also found that the flickering light boosted cognitive function in the mice, which performed much better on tests of spatial memory than untreated mice did.

In 2016 the Tsai lab showed that a week of 40 Hz visual stimulation for an hour a day induced gamma rhythms in the visual cortex and reduced toxic amyloid and tau proteins. These brain waves are believed to contribute to normal brain functions such as attention and memory, and previous studies have suggested they are impaired in AD patients.

Four months ago Tsai and her colleagues showed that combining the flickering light with audible 40 Hz tones reduced amyloid and tau even further and also had farther-reaching effects, extending to the hippocampus and parts of the prefrontal cortex. Auditory treatment improved cognition and memory.

In the new study, researchers found that visual stimulation, given one hour a day for three to six weeks (rather than just one week), had dramatic effects on neuron degeneration. They started the treatments shortly before degeneration would have been expected to begin, in two types of Alzheimer’s models. After

three weeks of treatment, “Tau P301S” mice showed no neuronal degeneration, while the untreated Tau P301S mice had lost 15 to 20 percent of their neurons. Neurodegeneration was also prevented in “CK-p25” mice, which were treated for six weeks.

To understand what was happening at a cellular level, the researchers analyzed differences in gene expression between treated and untreated mice, in both neurons and microglia — immune cells that are responsible for clearing debris from the brain.

In the neurons of untreated mice, the researchers saw a drop in the expression of genes associated with DNA repair, synaptic function, and another cellular process important for proper synapse function. Treated mice showed much higher expression of those genes than the untreated mice. The researchers also found higher numbers of synapses in the treated mice, as well as a greater degree of coherence (a measure of brain wave synchrony between different parts of the brain).

In their analysis of microglia, the researchers found that cells in untreated mice turned up their expression of inflammation-promoting genes, but the treated mice showed a striking decrease in those genes, along with a boost of genes associated with motility. This suggests that in the treated mice, microglia may be doing a better job of fighting off inflammation and clearing out molecules that could lead to the formation of amyloid plaques and neurofibrillary tangles, the researchers say. They also found lower levels of the version of the Tau protein that tends to form tangles.

■ In *Neuron*, Gamma Entrainment Binds Higher-Order Brain Regions and Offers Neuroprotection, May 7, 2019, <http://bit.ly/chinna-gamma>





Image caption: Shirley Weiss presents a poster about the research at the Picower Institute retreat.

## Glial Cells May Play Key Epilepsy Role

**A study provides potential new targets** for treating epilepsy and new fundamental insights into the relationship between neurons and their glial “helper” cells. In *eLife* April 26, Picower Institute scientists reported finding a key sequence of molecular events in which the genetic mutation in a fruit fly model of epilepsy leaves the flies vulnerable to stress-induced seizures.

About 60 million people worldwide have epilepsy, a neurological condition characterized by seizures resulting from excessive neural activity. The “zydeco” model flies in the study experience seizures in a similar fashion. Since discovering zydeco, the lab of MIT neurobiologist Troy Littleton, Menicon Professor in Neuroscience, has been investigating why the mutation makes it a powerful model of epilepsy.

Heading into the study, the team led by postdoc Shirley Weiss knew that the mutation was specifically expressed by cortex glial cells and that the protein it makes helps to pump calcium ions out of the cells. But that didn’t explain much about why a glial cell’s difficulty maintaining a natural ebb and flow of calcium ions would lead adjacent neurons to become too active under seizure-inducing stresses such as fever-grade temperatures or the fly being jostled around.

The activity of neurons rises and falls based on the flow of ions – for a neuron to “fire,” for instance, it takes in sodium ions, and then to calm back down it releases potassium ions. But the ability of neurons to do that depends on there being a conducive balance of ions outside

the cell. For instance, too much potassium outside makes it harder to get rid of potassium.

In a four-year series of experiments, Weiss, Littleton and their co-authors found that excess calcium in zydeco cortex glia cells causes them to hyper-activate a molecular pathway that leads them to withdraw many of the potassium channels that they typically deploy to remove potassium from around neurons. With too much potassium left around, neurons can’t calm down when they are excited.

“No one has really shown how calcium signaling in glia could directly communicate with this more classical role of glial cells in potassium buffering,” Littleton said. “So this is a really important discovery linking an observation that’s been found in glia for a long time – these calcium oscillations that no one really understood – to a real biological function in glial cells where it’s contributing to their ability to regulate ionic balance around neurons.”

Specifically, the research showed that hyper activation of calcineurin in zydeco glia led to an increase in a cellular process called endocytosis in which the cell was bringing too much of a protein called sandman back into the cell body. Without sandman staying on the cell membrane, the glia couldn’t effectively remove potassium from the outside.

When Weiss and her co-authors interfered to suppress endocytosis in zydeco flies, they were able to reduce seizures because that allowed more sandman to persist where it could reduce potassium. Sandman, notably, is equivalent to a protein in mammals called TRESK.

“Pharmacologically targeting glial pathways might be a promising avenue for future drug development in the field,” the authors wrote in *eLife*.

■ In *eLife*. Glial Ca<sup>2+</sup> signaling links endocytosis to K<sup>+</sup> buffering around neuronal somas to regulate excitability. April 26, 2019, <http://bit.ly/weiss-glial>

## PICOWER PEOPLE

### 5 from Picower honored as ‘Graduate Women of Excellence’

**As mentors, advocates, community** builders, educators, and leaders, five students in Picower Institute labs were honored April 29 by MIT’s Office of Graduate Education for looking beyond themselves and their research to support people around them.

**KAREN CUNNINGHAM**, who in the lab of Troy Littleton studies how the strength of neural connections called synapses varies, is a graduate resident advisor in the MacGregor House dorm. In that role, she is an embedded mentor for 45 undergraduates.

In the lab of Mark Bear, **JOYCE WANG** works to uncover mechanisms of learning and memory by studying how the brain processes vision. As she strives to improve the field’s understanding, she also teaches local K-12 students about neuroscience as a way of “giving back to the world.”

**KAREN GUADALUPE CRUZ**, the first in her family to be born in the U.S. and to graduate from college, works in the lab of Mriganka Sur to study the neuroscience of decision-making. Ever-mindful of support she has received in pursuing a PhD at MIT, she advocates within MIT and in Cambridge to build a more inclusive and supportive community for LGBT+ and minority students and residents.

Above the bustling crowd at the ceremony, quotes from each nomination graced a large screen.

“Scarlett is a deeply caring mentor,” read the testimonial about **SCARLETT BARKER**, whose research in the lab of Li-Huei Tsai investigates how some people remain cognitively resilient, even amid adversity such as Alzheimer’s disease pathology. “She is able to inspire urgency, creativity, excitement and collaboration. She is an inspiring scientist, leader and friend.”

**NICOLE APONTE SANTIAGO**, a member of the Littleton lab who studies how neurons that connect to the same cells interact to strengthen or weaken circuit connections, earned similar praise: “Apart from being hardworking, committed and highly excited about her research, she has also strived to help and inspire others who are pursuing or thinking about pursuing research. Nicole represents the best example of a graduate woman of excellence.”

# Retreat Offers a Chance to Soak in Research, and a Little Sun

More than 150 members of the Picower Institute gathered along Cape Cod's Atlantic shore June 3-4 to share their science (and hit the beach) at the end of another productive academic year.

The institute retreat in South Yarmouth, MA, provides researchers a chance to get away from heads-down daily tasks to learn from and appreciate each other's research. During the scientific program nine postdocs and graduate students gave talks and nearly two dozen more presented their work via posters. Joining them at the podium and poster session this year were keynote speaker Gord Fishell, a professor at Harvard Medical School, and several scientists visiting from the RIKEN Center for Brain Science in Japan.

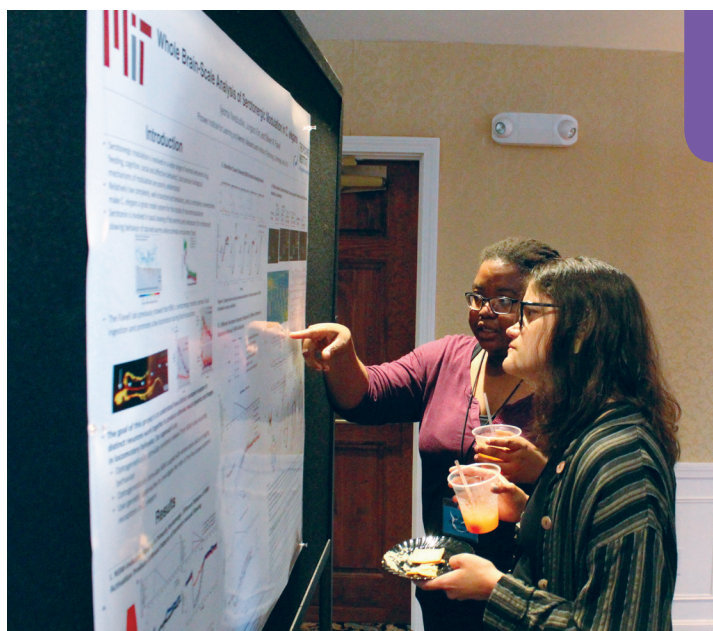
The rich information exchange covered topics as diverse as the brain itself, such as how the hippocampus encodes memories of our experiences and how advanced drug discovery and imaging techniques offer new ways to tackle disorders such as Rett syndrome.

Among many accomplished presenters, two Picower members earned honors: Tsai lab graduate student Scarlett Barker won the best talk award for her study of the underlying biology that allows some people to remain cognitively resilient, even when they have significant Alzheimer's pathology. Ijeoma Nwabudike, senior research support associate in the Flavell Lab, earned the best poster award for her study of how the neuromodulator serotonin works across the nervous system of the model organism *C. elegans*.

We extend many thanks to Wendy Fisher and siblings, whose 2008 gift in honor of their parents Dana and Betty Fisher helps to make Picower retreats possible each year.



Scarlett Barker presents her research on cognitive resilience



Ijeoma Nwabudike (left) discusses her poster on serotonin in *C. elegans*.

## PICOWER PEOPLE

At the 2019 University of Southern California commencement exercises, **EMERY N. BROWN**, Edward Hood Taplin Professor of Computational Neuroscience and Health Sciences & Technology at MIT, received an honorary Doctorate of Science (*honoris causa*). The university recognized Brown for his numerous breakthroughs in the field of anesthesiology, which include defining more accurately the brain's response to anesthetic

drugs and building new paradigms for monitoring patients under general anesthesia. He was also recognized for his statistics research, which has enhanced understanding of how neurons transmit and represent information in the brain. Brown was in good company. Other honorees included Congresswoman Karen Bass, renowned dancer and choreographer Mikhail Baryshnikov, and philanthropists Edythe and Eli Broad.

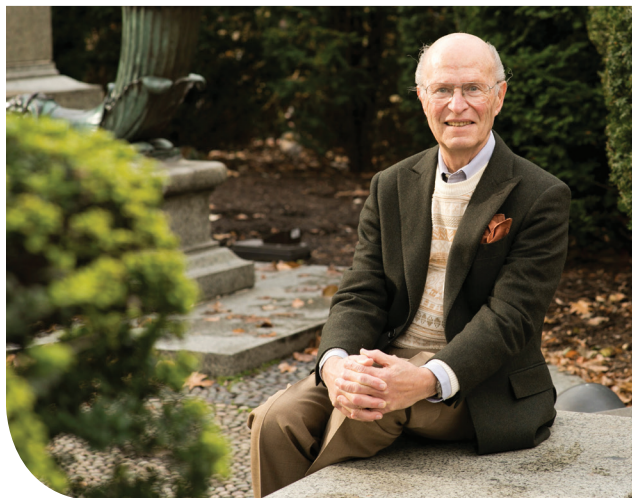
**STEVE FLAVELL**, Lister Brothers Career Development Assistant Professor, was one of four faculty members in the Department

of Brain and Cognitive Sciences to earn the department's recognition for superlative pedagogy and guidance to students. At the Hans-Lukas Teuber Lecture in March, Flavell received the BCS Teaching and Mentorship Award from department head Jim DiCarlo.

Two members of Picower Institute labs received School of Science awards for their service to colleagues. Tonegawa assistant lab manager **AREK HAMALIAN** earned an "Infinite Mile" award while postdoc **YEONG SHIN YIM** of the Choi lab won an Infinite Kilometer award.

# Impact of Giving

## Lester Gimpelson's Support of MIT Extends to Tsai lab Alzheimer's Research



**F**rom his childhood and through the MIT engineering education and telecommunications career that followed, Lester Gimpelson has maintained a passion for anthropology born of an empathy with the many peoples and communities he's encountered professionally and socially.

His affinity and advocacy for the people around him have been evident in the deep and culturally embracing ways he developed techniques for global technical marketing at the former telecomm giant ITT. His sensitive approach has also been evident in decades of service to MIT students as an Instructor, manager of MIT's admissions interviews in Belgium, and as the donor to his trust fund for undergraduate scholarships for first-generation and immigrant students. Recently he has extended his giving to support the Alzheimer's disease (AD) research of Picower Professor Li-Huei Tsai's lab after seeing friends suffer the disease's effects.

"I have known well several people who have gone under because of Alzheimer's disease, plus a contemporary of mine at MIT who was a very successful professor," Gimpelson said.

Gimpelson's generosity is helping Tsai mount a holistic, "whole-systems" investigation of Alzheimer's disease, which includes a comprehensive mapping of gene expression in the brain's many cell types (See page 3), rigorous modeling of how high-risk gene variants make the brain more susceptible to neurodegeneration and an innovative potential therapy that non-invasively stimulates gamma rhythms in the brain via the senses to mount a powerful response to the disease (p. 2).

### From MIT to BTL to ITT

Gimpelson is no stranger to innovation and the research it requires. At MIT he earned three electrical engineering degrees focusing on communications, and settled on statistical communications, a discipline for extracting useful data from weak and noisy signals.

With that training, Gimpelson worked at the leading U.S. research laboratory, BTL, first redesigning national telephone networks to relieve traffic congestion and then developing programs to design them. In 1968, he joined ITT's Belgian headquarters where he directed areas of their European R&D laboratories, first expanding telephone facilities to carry data and then developing a fusion of

engineering and highly technical marketing for very large systems.

Ever the "amateur anthropologist," he said, his international work included learning local cultures and befriending the people he'd work with on multi-year projects.

### MIT Engagement

Gimpelson has also remained engaged with the MIT community for the long-term. From 1959 to 1961 he was an award-winning Instructor and an early advocate of including writing and public speaking training in MIT's core curriculum. For years he managed MIT applicants' interviews in Belgium, following many accepted students through their undergraduate years.

And, eager to help students who, like himself, are the first in their families to attend college, Gimpelson now funds scholarships.

"There's a great reward for me," he said. "The words: 'I just couldn't be here without it,'"

He also remains connected to MIT as a lifelong learner. He frequently attends faculty lectures. That's where he first became inspired by Tsai's research.

### Research Impact

Tsai said Gimpelson's contributions have been vital in supporting her research, which has reached important milestones this year. In three recent papers, her lab has reported substantial progress, including showing that the gamma rhythm stimulation approach preserves memory in mice and prevents neurons from dying.

Gimpelson said he is especially intrigued by this line of research, while realizing that all the published results so far have occurred in mice. Gimpelson said he is hopeful that the same benefits will emerge in humans. That's why he's glad to be helping fund the testing.

"The testing we have begun in humans is absolutely essential," Tsai said. "A lot of things that work in mice don't turn out to work in people. But we can try our best ideas, and we are very grateful to Lester for helping ensure that we have the resources to do that."

In the meantime, Gimpelson said, with no effective AD drug treatments available, Tsai's work to develop a different approach is important both because of its possible therapeutic benefit, and because it's not based on pills or implants.

"We all know the outcome we want from the research," he said. "I'm fascinated by it and the fact that it's non-invasive is setting the whole field in an exciting new direction."

Gimpelson's philanthropy has been a key reason it's been moving ahead.

# Gift Creates Broderick Fund for Phytocannabinoid Research



**C**harles R. Broderick, an alumnus of MIT and Harvard University, has made gifts to both alma maters to support fundamental research into the effects of cannabis on the brain and behavior.

The gifts, totaling \$9 million, represent the largest donation to date to support independent research on the science of cannabinoids. The donation will allow experts in the fields of neuroscience and biomedicine at MIT and Harvard Medical School to conduct research that may ultimately help unravel the biology of cannabinoids, illuminate their effects on the human brain, catalyze treatments, and inform evidence-based clinical guidelines, societal policies, and regulation of cannabis.

## Lagging Behind Legislation

With the increasing use of cannabis both for medicinal and recreational purposes, there is a growing concern about critical gaps in knowledge.

In 2017, the National Academies of Sciences, Engineering, and Medicine issued a report calling upon philanthropic organizations, private companies, public agencies and others to develop a “comprehensive evidence base” on the short- and long-term health effects — both beneficial and harmful — of cannabis use.

Broderick is the founder of Uji Capital LLC, a family office focused on quantitative opportunities in global equity capital markets. Identifying the growth of the Canadian legal cannabis market as a strategic investment opportunity, Broderick has taken equity positions in several companies in the emerging business.

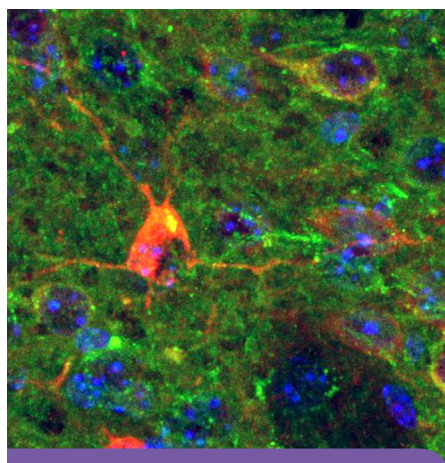
Through the Broderick gifts to Harvard Medical School and MIT’s School of

Science through the Picower Institute for Learning and Memory and the McGovern Institute for Brain Research, the Broderick funds will support independent studies of the neurobiology of cannabis; its effects on brain development, various organ systems and overall health, including treatment and therapeutic contexts; and cognitive, behavioral and social ramifications.

“I want to destigmatize the conversation around cannabis — and, in part, that means providing facts to the medical community, as well as the general public,” says Broderick, who argues that independent research needs to form the basis for policy discussions, regardless of whether it is good for business. “Then we’re all working from the same information. We need to replace rhetoric with research.”

## MIT: Focused on Brain Health and Function

The gift to MIT from Broderick will provide \$4.5 million over three years to support independent research for four scientists at the Picower and McGovern institutes.



Staining of cells in the nucleus accumbens of a mouse highlights specific cell types that will be of interest in the Heiman lab’s study of how exposure to cannabis during adolescence might relate to the development of schizophrenia. Image: Amanda Vernon.

Two of these researchers — Myriam Heiman, the Latham Family Associate Professor of Neuroscience at the Picower Institute and John Gabrieli, the Grover Hermann Professor of Health Sciences and Technology, a professor of brain and cognitive sciences at the McGovern Institute will each explore the relationship between cannabis and schizophrenia.

Heiman, who is a molecular neuroscientist, will study how chronic exposure to phytocannabinoid molecules THC and CBD in mouse models may alter the developmental molecular trajectories of cell types implicated in schizophrenia.

“Our lab’s research may provide insight into why several emerging lines of evidence suggest that adolescent cannabis use can be associated with adverse outcomes not seen in adults,” says Heiman.

Gabrieli will monitor any potential therapeutic value of cannabis for adults with schizophrenia using fMRI scans and behavioral studies.

In addition to these studies, Gabrieli also will investigate whether cannabis can have therapeutic value for autism spectrum disorders, and Heiman plans to look at whether cannabis can have therapeutic value for Huntington’s disease.

Earl Miller, Picower Professor of Neuroscience at the Picower Institute, will study effects of cannabinoids on both attention and working memory. His lab has recently formulated a model of working memory and unlocked how anesthetics reduce consciousness, showing in both cases a key role in the brain’s frontal cortex for brain rhythms, or the synchronous firing of neurons. He will observe how these rhythms may be affected by cannabis use — findings that may be able to shed light on tasks like driving where maintenance of attention is especially crucial.

“My life’s goal is to understand the neural basis of cognition,” Miller said. “Cannabis can provide a window into that because it changes cognition. This opportunity is also important because it is not easy to get funding to study cannabis. Private funding allows us to ask questions we wouldn’t otherwise get to ask.”

McGovern Institute Professor Ann Graybiel has proposed to study the cannabinoid 1 (CB1) receptor, which mediates many of the effects of cannabinoids. Her team recently found that CB1 receptors are tightly linked to dopamine — a neurotransmitter that affects both mood and motivation.



## Neuroscientists Look To The Body To Better Understand The Brain

**I**t turns out that understanding the brain, with its hundreds of billions of cells and trillions of circuit connections, also requires looking at the heart, and following the winding path of the intestine. In fact, as Picower Institute research is helping to show, neuroscience not only has to go beyond the nervous system, but also to cells that aren't even part of the same organism that the nervous system belongs to. The colonies of bacteria that we host — our “microbiome” — appear to exert a mysterious and multifaceted influence on our mental function and health.

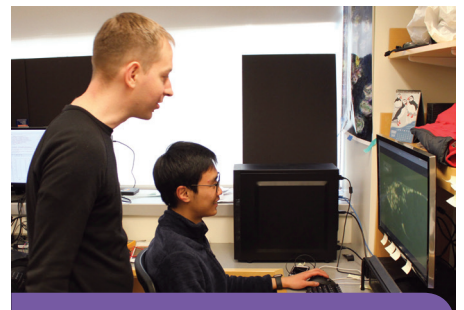
In other words, the rest of the body has a lot to teach us about the brain. That's why three Picower Institute professors — Emery Brown, Gloria Choi and Steve Flavell — are looking below the neck to get a better view inside the head.

### Going with the Gut

Flavell is investigating communication between the brain and body using the nematode worm *C. elegans*. But what he has found in that simple creature's alimentary canal may help explain a great deal about how our mood changes with our sense of satiety, and one of the main ways that the bacterial microbiome communicates with the brain.

In a paper in *Cell* earlier this year, Flavell's lab discovered the function of two genes — also expressed in the intestines of humans — at the nexus of how the worm senses that it has happened up on a yummy lunch of bacteria and should slow its movement to slurp up the meal. The finding represents a significant leap in connecting bacterial sensing in the gut with behavior, providing clues about how the gut and brain might communicate in people, too.

In 2013 Flavell had identified an important role in behavioral regulation for a *C. elegans* neuron named “NSM,” which extends dendrites into the alimentary canal. He showed that when a worm is eating, the neuron emits the neurotransmitter serotonin to signal to other neurons. In the new paper, he showed that this all depends on the neuron deploying two acid sensing ion channels (ASICs) called DEL-3 and DEL-7, encoded by those newly characterized genes. These ASICs appear to be critical for NSM's detection of bacteria in the alimentary canal. There is still much more he wants to learn, including exactly what chemicals the bacteria emit to trigger the neuron, whether there are other DELs that sense other bacterial substances, and whether other neurons express as yet uncharacterized channels, too. Moreover, there is still plenty to know about how neurotransmitters emanating from the



Steve Flavell (standing) works in the lab with graduate student Jungsoo Kim to study serotonin's effect on the brain.

gut, like serotonin, influence the brain to affect behavior, in both the worm and in people.

The answers have wide-ranging implications. Earlier this year, a broad epidemiological study found widespread, specific associations between differences in gut microbiome bacterial populations and the likelihood that individuals suffer from mental health concerns such as autism and depression.

“There appear to be specific types of gut bacteria that are overrepresented and underrepresented in humans that suffer from these disorders,” Flavell said. “These types of data make the case that there is at least a correlation between the bacteria that live in our gut and our complex behaviors.”

Flavell's work could help explain exactly how those associations arise.

### Immune Communication

Gloria Choi is also minding the mechanisms linking the microbiome to the brain, but in



a different way. Her research investigates the surprising proposition that the immune system directly impacts the nervous system. Immune system cells communicate by secreting proteins called cytokines. These, she has found, can also affect neurons in the brain.

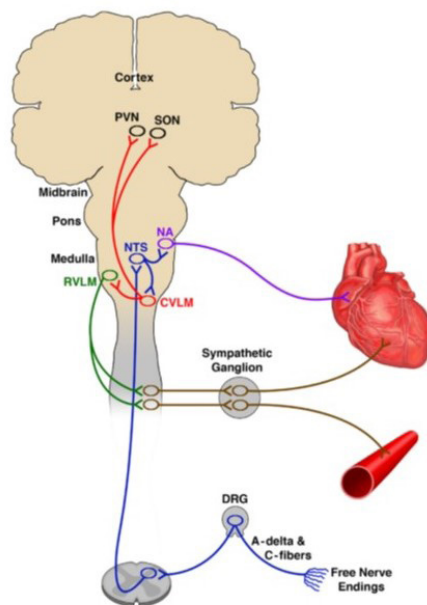
It makes sense that this could be the case. Immune system cells are sentinels of health. Perhaps the immune system is an efficient messenger for the brain about aspects of the body's status.

Suggestive links are everywhere. Our mood and behavior change when we are sick, and there are often mood-related side effects to medications that affect the immune system. Like Flavell, Choi is on the forefront of showing detailed, tangible cause-and-effect evidence, which the field has rightly demanded.

“The primary goal of my research program is to elucidate the mechanisms through which the immune system modulates neural circuit function, ultimately shaping animal behavior,” Choi said.

She did exactly that in three papers linking infection in pregnant mice with neurodevelopmental symptoms in their offspring. In a 2016 paper in *Science*, she and collaborators showed that a particular type of immune cell and its secretion of the cytokine interleukin-17a (IL-17a), mediated the mother mouse's immune system activation and the development of autism-like behavioral abnormalities in offspring. The next year, the collaboration followed with a tandem of papers in *Nature*. One showed the phenomenon was further mediated by the presence of maternal intestinal bacteria that promote differentiation of the implicated immune cells. The other showed that the effect of IL-17a in the brain was focused in the S1DZ region of the cortex where they observed dysregulated neural activity. The team showed that by intervening to reduce excess neural activity, they could mitigate behavioral abnormalities associated with maternal infection.

Choi continues to study instances of immune system influence on the nervous system and modulation of this interaction by constituents of the gut microbiome. Understanding fundamentals of this tripartite relationship, she said, might lead to ways to prevent or mitigate mental health problems possibly by means involving the



Emery N. Brown's diagram of the medullary nociceptive autonomic circuit, which routes damage signals to the brain and routes sympathetic responses to the heart and vasculature.

immune system or the gut microbiome. To her the potential contributions she can make to fundamental science and the ability to inform treatment of disease are each intensely motivating.

## Knowing Nociception

It might seem intuitive that Emery N. Brown studies heart rate and blood pressure. He is, after all, not only a MIT neuroscientist, but also a Massachusetts General Hospital anesthesiologist, and for decades anesthesiologists have used such apparently non-neural bellwethers to assess consciousness in patients. But that's where the surprise comes in. Brown is actually changing the way anesthesia is administered by investigating the connection of those responses back to the brain.

Brown studies the circuits that sense damage to the body, or “nociception,” and relay that information to the brain. When you are conscious, the body's nociception system warnings are experienced as pain, but even when you are

unconscious it is still working. Via one particular circuit, the brain then directs the “sympathetic” responses detected in the circulatory system. Brown calls that circuit the medullary nociceptive autonomic circuit.

“This should be anesthesiology 101,” Brown said. “This is the sacred circuit.”

Brown is interested in nociception because his research shows that it should be the central focus of dosing and administering anesthetic drugs. Managing nociception means properly suppressing pain. His careful study of the diversity of circuits involved in processing nociception has led to the crucial insight, published last year in *Anesthesia and Analgesia*, that by targeting them with low doses of different antinociceptive drugs – a custom cocktail he conceives for each patient – he can provide better nociception and pain management, limiting the use of opioids. Meanwhile, because many of these drugs also reduce consciousness, he can radically scale back the amount of drug needed for that. Patients wake up more quickly and less groggy, a significant benefit for old and young patients who are subject to post-operative delirium.

On day in May, still in the operating room right after a bladder surgery at MGH, a patient woke up and said, “We're good,” Brown said. His rapid return to lucidity was the product of using much less drug for unconsciousness.

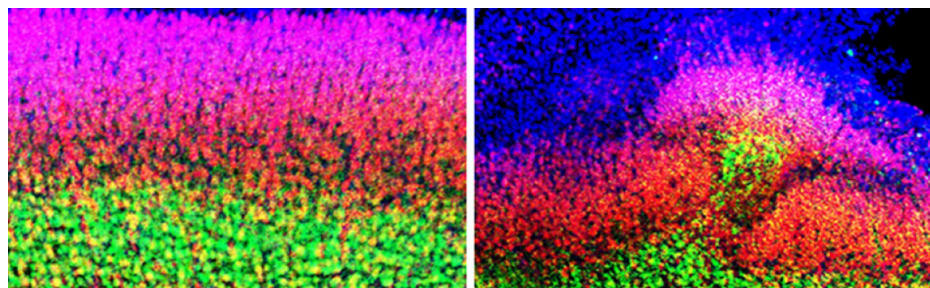
“Up until three years ago, this wasn't how I practiced, but we've come to a deeper appreciation of nociception,” he said.

In the OR, Brown carefully monitors consciousness in the brain by reading out EEGs (another innovative practice), and he also still uses those traditional methods of reading out heart rate and blood pressure. By studying the medullary nociceptive autonomic circuit he's also hoping to have a refined method for monitoring nociception. There is currently no model for doing so.

To change that, graduate student Sandya Subramanian is dedicating her thesis research to studying the circuit and measuring these circulatory system and other responses during surgery, and in normal awake and low-stress states as a baseline. Deriving an objective biomarker of nociceptive response will help refine anesthesia dosing strategy even further.

Ultimately, anesthesia acts on the brain, but understanding that fully requires looking to the body. Like Flavell and Choi, Brown is studying the brain by looking beyond it.

The Choi Lab found that *in utero* exposure of the brain to the immune cell cytokine IL-17a resulted in abnormal cortical development (on right).



# Newly Installed Paintings Seek to Investigate, Inspire



**T**odd Siler's six-painting series, "A.R.T.strings," newly installed along the Picower Institute's main third-floor corridor, investigates the myriad connections between the brain and nature both as we experience them and as we understand them.

Broadly encompassing in their representations, the works are tethered to objective phenomena yet unconstrained in their inspiration, message and form. In presenting the series, Siler spells out art as an acronym standing for "All Representations of Thought" and he couples neuroscience and cognition with reference to nature at its most fundamental and universal level, the multidimensional physics "string theory" of everything.

In each painting, Siler intertwines many conceptual dimensions. Consider the fifth in the series, "Surging Anxiety: The Painted Wall" at Black Canyon," inspired by the overwhelming wonder he felt amid the towering Colorado landform. Siler represents different scales of natural forms – features of the canyon, such as a gravely patch along the river bed, and the brain, such as the four axon terminals that slant down the canvas like the canyon walls. In the context of a chasm carved over eons, he captures feelings and memories formed within seconds. Like time and the canyon's spatial vastness, the complex information of the canyon is compressed within the brain, and in Siler's painting emotion is, too: The vertically stretched word "anxiety" lies nestled among the axon terminals, as if anticipating a chance discovery.

Similarly the first painting in the series, "Cerebral Flares of Unfathomable Influences," mixes printed and painted media to abstract parallels between diverse natural phenomena:

solar flares and surges of feeling. Siler calls this connection "Processmorphology: the comparative study of processes in like and unlike systems."

As physical forms, the paintings exhibit a free sense of inquiry. They are neither framed nor regularly quadrilateral and the materials venture outward from the canvas, often with a delicate sculpturing that allows them to move with the ambient air.

Siler has been inspired by the brain, particularly as the source of creativity and innovation, since childhood and has long made it the central theme of his art. The people, scholarship and technologies he encountered at MIT, where he became the first visual artist to earn a PhD in 1986, continue to influence his work as well. A.R.T.strings accompanies an earlier installation of his works at the Picower Institute.

A.R.T.strings comes to Picower as a donation from Siler's longtime friend D.A. Duke, on behalf of the Duke Family of Denver. Siler said he is excited that his art exists in intimate intersection with the daily work of MIT neuroscientists.

"The art is meant to be catalytic and to cultivate the kind of innovative thinking that happens when someone is walking on the way from one place to another and stops to 'Artgaze' – suddenly realizing: I never thought about art and the brain that way," he said. "That starts the 'ArtScience' process of creative-critical thinking about the bigger picture of their work, and other things they could add or relate that might enrich their research."





(Top to bottom) Artist Todd Siler holds his painting 'Drumming Primordial Rhythms of the Cosmos' on the wall of the Picower Institute's third-floor corridor as an installer consults on its placement; An installer puts the finishing touches on the placement of 'Surging Anxiety: The Painted Wall at Black Canyon'; Detail from 'Cerebral Flares of Unfathomable Influences';

**Picower Institute Fall Symposium**  
**Oct. 16, 2019 - MIT Building 46**

# Neural Mechanisms of Memory and Cognition

<p><b>Jessica Cardin</b> Yale University</p>	<p><b>Michael Halassa</b> MIT</p>	<p><b>Alvaro Pascual-Leone</b> Beth Israel Deaconess Medical Center / Harvard</p>
<p><b>Diane Chan</b> Picower Institute at MIT</p>	<p><b>Christopher Harvey</b> Harvard University</p>	<p><b>Mu-ming Poo</b> Institute of Neuroscience, Shanghai</p>
<p><b>Martin Fuhrmann</b> German Center for Neurodegenerative Diseases</p>	<p><b>Thomas McHugh</b> RIKEN Center for Brain Science</p>	<p><b>Andreas Schaefer</b> Francis Crick Institute</p>
<p><b>Lisa Giocomo</b> Stanford University</p>	<p><b>Elly Nedivi</b> Picower Institute at MIT</p>	

Save the date - Nov. 6, 2019

Inaugural Alana Down Syndrome Center Symposium

## Translational Research in Down Syndrome

Keynote speakers



- **Roger Reeves**, McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University
- **Joaquin Espinosa**, Linda Crnic Institute for Down Syndrome, University of Colorado

Picower Institute - MIT Building 46

### October 7

#### *Aging Brain Seminar*

**BING REN**  
Ludwig Cancer Research,  
UC San Diego

Ren's lab is devoted to the identification and characterization of the transcriptional regulatory code of the human genome. This regulatory code mediates the controlled expression of specific subsets of genes in a particular cell type, developmental stage, disease state or environmental response. Determining this code, he says, has profound implications for our understanding of human evolution, development and disease processes.



## Neuroscience News // Summer 2019



### OUR VISION

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.

### 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:  
Asha Bhakar, PhD, [abhakar@mit.edu](mailto:abhakar@mit.edu), Tel: 617-258-0759.

### HOW TO SUBMIT & SUBSCRIBE

Subscriptions to Neuroscience News are available at no charge in print or PDF form. To subscribe or submit story ideas and comments, send your mailing or email address to: David Orenstein, [davidjo@mit.edu](mailto:davidjo@mit.edu), Tel: 617-324-2079

### EDITORIAL CONTRIBUTORS

David Orenstein, Anne Trafton and Julia Keller

### CONTACT THE PICOWER INSTITUTE

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](http://picower.mit.edu)

**TOP ROW:** **Mark F. Bear**, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Investigator, Howard Hughes Medical Institute (HHMI); **Emery Brown**, Edward Hood Taplin Professor of Computational Neuroscience and Health Sciences & Technology, The Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology; **Gloria Choi**, Samuel A. Goldblith Career Development Assistant Professor of Applied Biology, Department of Brain and Cognitive Sciences; **Kwanghun Chung**, Assistant Professor, Departments of Chemical Engineering and Brain and Cognitive Sciences, Institute of Medical Engineering and Science core faculty; **Steven Flavell**, Lister Brothers Career Development Assistant Professor of Neuroscience, The Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology; **Myriam Heiman**, Associate Professor of Neuroscience, Department of Brain and Cognitive Sciences, Broad Institute core member; **Troy Littleton**, Menicon Professor of Biology and Neuroscience, Departments of Biology and Brain and Cognitive Sciences.

**BOTTOM ROW:** **Earl Miller**, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences; **Elly Nedivi**, William R. (1964) & Linda R. Young Professor of Neuroscience, The Picower Institute for Learning and Memory, 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; **Matthew Wilson**, Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology, Associate Director, The Picower Institute for Learning and Memory.

Choi photo by Justin Knight