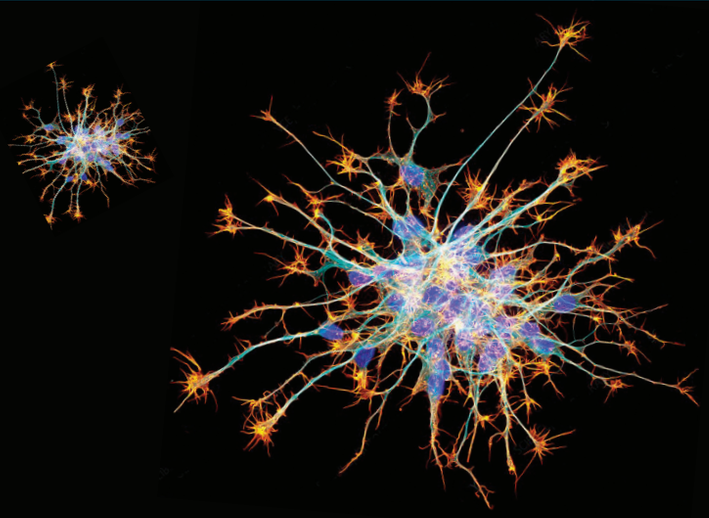
INSIDE

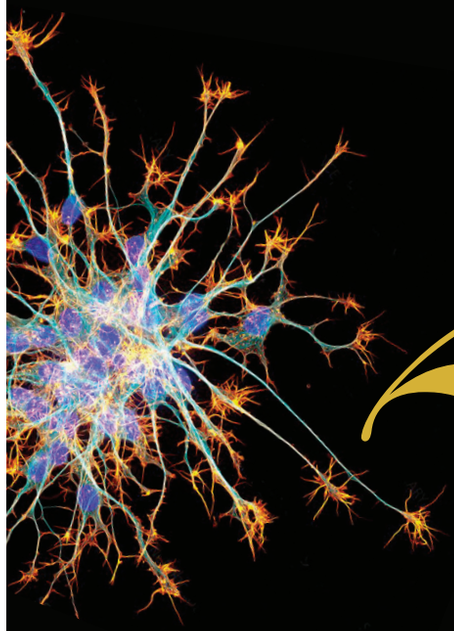


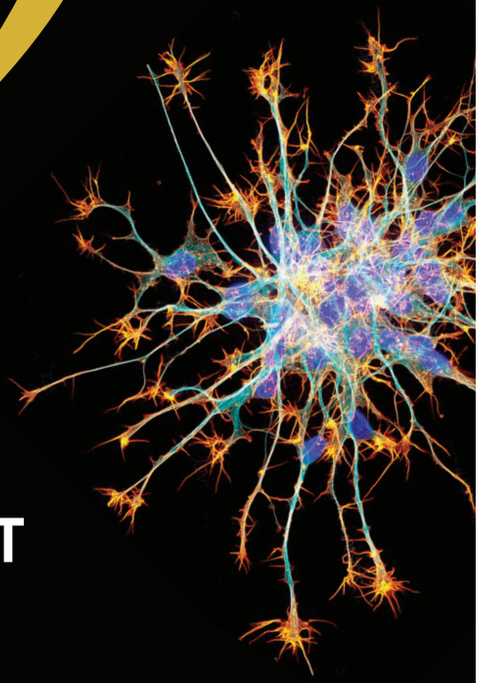
THE PICOWER INSTITUTE

2002 - 2022

20 years

OF DISCOVERY AND IMPACT



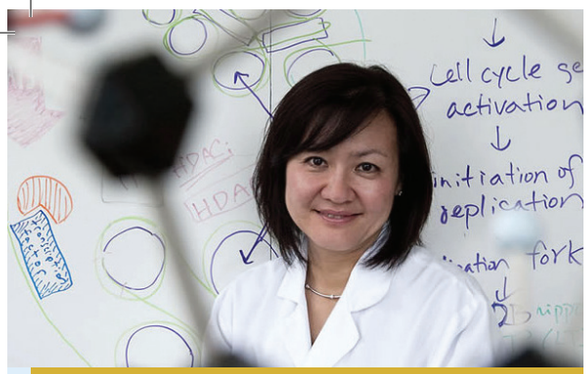


Neuroscience News

MIT SUMMER 2022

THE PICOWER INSTITUTE FOR LEARNING AND MEMORY

20 years OF DISCOVERY & IMPACT



DIRECTOR'S **MESSAGE**

Dear Friends,

In May 2002, when MIT received a transformative donation from The Picower Foundation, a bright future of brain science research dawned.

The gift from Barbara and Jeffry Picower elevated our research, facilities and operations to the level of a leading neuroscience institute. Ongoing support from the JPB Foundation, the Picower Foundation's successor, has continued alongside other philanthropic gifts to enable excellence in our research and training.

As we mark 20 years we are embracing the opportunity to reflect on why we do this work, where we began, what have we discovered, what impact that's had, and what's next.

Normally in *Neuroscience News* we tell this ongoing story by its individual moments, with news updates and a deeper look at a single hot topic. But in this special edition we take a step back to look at the arc of this whole, continuing 20-year endeavor by telling the stories of our faculty in one-page profiles (p. 9). You can get to know us through these pieces—learn what drives us, where that's taken us, and where we may be headed. You can learn the personal context of our work. We hope that you will come to share our excitement about exploring the brain in health and disease at least a little more.

Importantly, each story is illustrated not only with our pictures but with a recent group photo of each lab. Science is teamwork and the greatest privilege of being at MIT is the chance to collaborate with and to help train the brilliant students and research staff who choose to come here. These stories couldn't represent our work without also representing them.

You can engage with all of us not only by reading on, but also by joining us in person or online on Sept. 22 for our 20th Anniversary Exhibition (p. 23). We hope to celebrate with you then.

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

How **surprise** helps us learn

Timely and spatially tuned releases of noradrenaline from the locus coeruleus (LC) region help the brain learn from surprising outcomes, a new MIT study finds.

Noradrenaline has been linked to arousal and boosting alertness, and too much noradrenaline can lead to anxiety. Previous studies of the LC have shown that it receives input from many parts of the brain and also sends its signals far and wide. In the new study, the researchers revealed its role in a type of learning called reinforcement learning, or learning by trial and error.

Mriganka Sur, Newton Professor of Neuroscience, is senior author of the paper in *Nature*. Vincent Breton-Provencher, a former MIT postdoc who is now an assistant professor at Laval University, and Gabrielle Drummond, an MIT graduate student, are the lead authors.

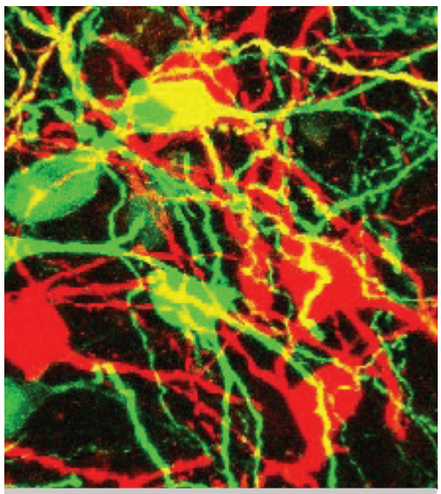
The team trained mice to push a lever when they heard a high-frequency tone, but not when they heard a low-frequency tone. When the mice responded correctly to the high-frequency tone, they received a water reward, but if they pushed the lever when they heard a low-frequency tone, they received an unpleasant puff of air.

The mice learned to push the lever harder when the tones were louder. When the volume was lower, they were more uncertain about whether they should push or not. And, when the researchers inhibited activity of the LC, the mice became much more hesitant to push the lever when they heard low volume tones, suggesting that noradrenaline promotes taking a chance on getting a reward in situations where the payoff is uncertain.

"The animal is pushing because it wants a reward, and the locus coeruleus provides critical signals to say, push now, because the reward will come," Sur says.

The researchers also found that the neurons that generate this noradrenaline signal appear to send most of their output to the motor cortex, which offers more evidence that this signal stimulates the animals to take action.

While that initial burst of noradrenaline appears to stimulate the mice to take action, the researchers also found that a second burst often occurs after the trial is finished. When the mice received an expected reward, these bursts were small.



Neurons of the locus coeruleus. Red ones project to the motor cortex. Green ones project to the prefrontal cortex.
Image by Gabi Drummond

However, when the outcome of the trial was a surprise, the bursts were much larger. For example, when a mouse received a puff of air instead of the reward it was expecting, the LC sent out a large burst of noradrenaline.

In subsequent trials, that mouse would be much less likely to push the lever when it was uncertain it would receive a reward. "The animal is constantly adjusting its behavior," Sur says. "Even though it has already learned the task, it's adjusting its behavior based on what it has just done."

The mice also showed bursts of noradrenaline on trials when they received an unexpected reward. These bursts appeared to spread noradrenaline to many parts of the brain, including the prefrontal cortex, where planning and other higher cognitive functions occur.

"The surprise-encoding function of the LC seems to be much more widespread in the brain, and that may make sense because everything we do is moderated by surprise," Sur says.

The researchers now plan to explore the possible synergy between noradrenaline and other neuromodulators, especially dopamine, which also responds to unexpected rewards. They also hope to learn more about how the prefrontal cortex stores the short-term memory of the input from the LC to help the animals improve their performance in future trials.

A single **memory** is stored across many connected brain regions

A new study by scientists at The Picower Institute provides the most comprehensive and rigorous evidence yet that the mammalian brain stores a single memory across a widely distributed, functionally connected complex spanning many brain regions, rather than in just one or even a few places.

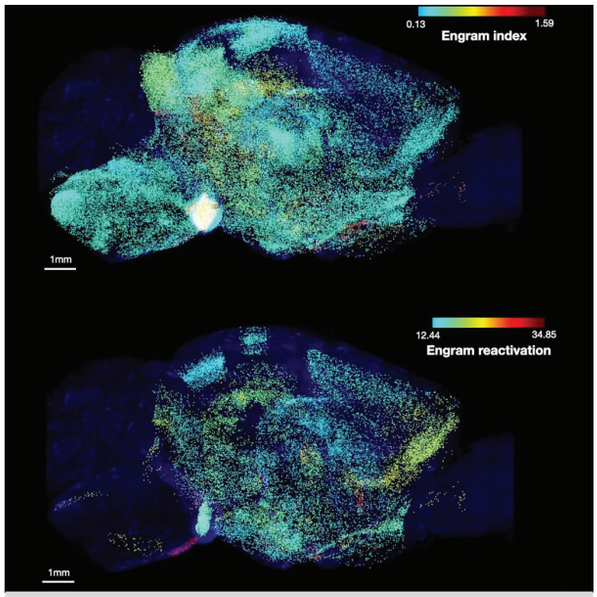
The team identified and ranked dozens of areas that were not previously known to be involved in memory and showed that memory recall becomes more behaviorally powerful when multiple memory-storing regions are reactivated, rather than just one.

"When talking about memory storage we all usually talk about the hippocampus or the cortex," said co-lead and co-corresponding author Dheeraj Roy. He began the research while a graduate student in the RIKEN-MIT Laboratory for Neural Circuit Genetics at The Picower Institute led by senior author and Picower Professor Susumu Tonegawa. "This study reflects the most comprehensive description of memory encoding cells, or memory 'engrams,' distributed across the brain, not just in the well-known memory regions. It basically provides the first rank-ordered list for high-probability engram regions. This list should lead to many future studies, which we are excited about, both in our labs and by other groups."

In addition to Roy, who is now a McGovern Fellow in the Broad and McGovern Institutes, the study's other lead authors are Young-Gyun Park, Minyoung Kim, Ying Zhang and Sachie Ogawa.

The team mapped regions participating in an engram complex by analyzing 247 brain regions in mice who were taken from their comfortable home enclosure to a novel enclosure where they felt a small but memorable electrical zap. In one group of mice their neurons were engineered to become fluorescent when they expressed a gene required for memory encoding. In another group, cells activated by naturally recalling the unpleasant memory (e.g. when the mice returned to the scene of the zap) were fluorescently labeled instead.

Cells that were activated by memory encoding or by recall could therefore readily be seen under a microscope after the brains were preserved and optically cleared using a technology called SHIELD, developed by co-corresponding author Kwanghun Chung, Associate Professor in The Picower Institute. By using a computer to count fluorescing cells in each sample, the team produced brain-wide maps of regions with apparently significant memory encoding or recall activity.



Across the mouse brain (top) cells are color coded by likelihood of being involved in a memory engram. On bottom cells are labeled by their reactivation during memory recall.

This allowed them to calculate an "engram index" to rank order 117 brain regions with a significant likelihood of being involved in the memory engram complex. They deepened the analysis by engineering new mice in which neurons involved in both memory encoding and in recall could be doubly labeled, thereby revealing which cells exhibited overlap of those activities.

To really be an engram cell, the authors noted, a neuron should be activated both in encoding and recall. "These experiments not only revealed significant engram reactivation in known hippocampal and amygdala regions, but also showed reactivation in many thalamic, cortical, midbrain and brainstem structures," the authors wrote.

Having ranked regions, the team engaged in several manipulations to directly test their predictions and to determine how engram complex regions might work together.

For instance, they engineered mice such that cells activated by memory encoding would also become controllable with flashes of light (a technique called "optogenetics").

The researchers then applied light flashes to select brain regions from their engram index list to see if activating those would artificially reproduce the fear memory behavior of freezing in place, even when mice were placed in a "neutral" enclosure where the zap had not occurred.

"Strikingly, all these brain regions induced robust memory recall when they were optogenetically stimulated," the researchers observed. Moreover, stimulating areas that their analysis suggested were insignificant to the unpleasant memory indeed produced no freezing behavior.

The team then demonstrated how different regions within an engram complex connect. And further experiments showed that stimulating up to three involved regions simultaneously produced more robust freezing behavior than stimulating just one or two.

Roy said that by storing a single memory across such a widespread complex the brain might be making memory more efficient and resilient.

"Different memory engrams may allow us to recreate memories more efficiently when we are trying to remember a previous event (and similarly for the initial encoding where different engrams may contribute different information from the original experience)," he said. "Secondly, in disease states, if a few regions are impaired, distributed memories would allow us to remember previous events and in some ways be more robust against regional damages."

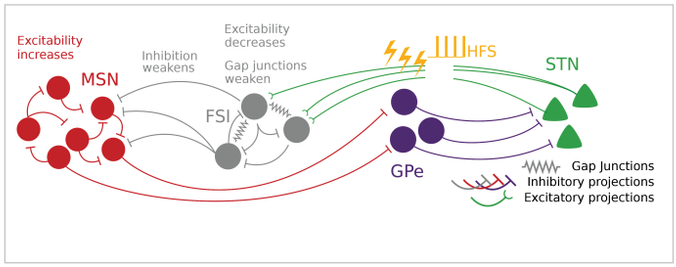
Modeling how deep brain stimulation treats **Parkinson's** disease symptoms

Parkinson's disease poses many mysteries, including exactly how deep brain stimulation (DBS) relieves some of the motor symptoms patients experience. In a new study, scientists at Boston University and The Picower Institute present a detailed model explaining the underlying circuit dynamics, providing an explanation that, if experimentally confirmed, could improve the therapy further.

Among the things that are known about Parkinson's disease is that a deficit of the neuromodulator dopamine is associated with abnormally high beta-frequency rhythms (brain waves at a frequency of about 20 Hz). DBS, involving the delivery of high-frequency electrical stimulation to a region called the subthalamic nucleus (STN), apparently suppresses these elevated beta rhythms, restoring a healthier balance with other rhythm frequencies and better movement control.

The new biophysically-based computational model described in the *Proceedings of the National Academy of Sciences* posits that the beneficial effect of DBS arises from how it interrupts a vicious cycle promoting runaway beta in a circuit loop between the STN and a region called the striatum.

The new model, led by Picower Institute postdoc Elie Adam, builds on prior work by Michelle McCarthy, research assistant professor of mathematics and statistics at BU. Joining Adam and McCarthy are co-authors Emery N. Brown, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience at MIT and Nancy Kopell, professor of mathematics and statistics at BU. Their model posits that under healthy conditions, with adequate dopamine, cells in the striatum called fast-spiking interneurons (FSIs) produce gamma-frequency rhythms (30-100 Hz) that regulate the beta activity of medium spiny neurons (MSNs). But without dopamine, the FSIs are unable to



limit the MSN activity and beta comes to dominate a whole circuit loop connecting the STN to the FSIs, to the MSNs, to other regions and then back to the STN. When DBS high-frequency stimulation is applied to the STN, the model shows, that replaces the overwhelming beta input received by the FSIs and restores their excitability. Reinvigorated and freed from those beta shackles, the interneurons resume producing gamma oscillations (at about half the DBS stimulation frequency, typically at 135 Hz) that then suppress the beta activity of the MSNs.

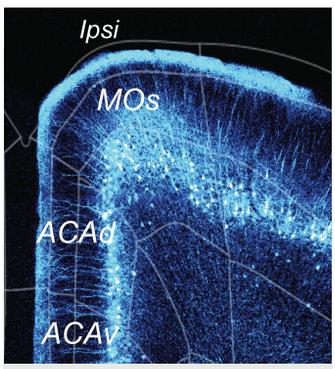
Circuit that focuses **attention** has widespread inputs

In a new brain-wide circuit tracing study, scientists at The Picower Institute focused selective attention on a circuit that governs, fittingly enough, selective attention. The comprehensive maps they produced illustrate how broadly the mammalian brain incorporates and integrates information to focus its sensory resources on its goals.

Working in mice, the team traced thousands of inputs into the circuit, a communication loop between the anterior cingulate cortex (ACC) and the lateral posterior (LP) thalamus. In primates the LP is called the pulvinar. Studies in humans and non-human primates have indicated that the byplay of these two regions is critical for brain functions like being able to focus on an object of interest in a crowded scene, said study co-lead author Yi Ning Leow, a graduate student in the lab of senior author Mriganka Sur, Newton Professor of Neuroscience. Research has implicated dysfunction in the circuit in attention-affecting disorders such as autism and ADHD.

The new study in the *Journal of Comparative Neurology* extends what's known about the circuit by detailing it in mice, Leow said, importantly showing that the mouse circuit is closely analogous to the primate version.

"In these rodent models we were able to find very similar circuits," Leow said. "So we can possibly study these higher order functions in mice as well. We have a lot more genetic tools in mice so we are better able to look at this circuit."



Neurons that project to the lateral posterior thalamus are visible in the ACC regions of a mouse's brain (ACAd & ACAv).
Image by Ning Leow

The study, also co-led by former MIT undergraduate Blake Zhou, therefore provides a detailed roadmap in the experimentally accessible mouse model for understanding how the ACC and LP cooperate to produce selective attention. For instance, now that Leow and Zhou have located all the inputs that are wired into the circuit, Leow is tapping into those feeds to eavesdrop on the information they are carrying. Meanwhile, she is correlating that information flow with behavior.

"This study lays the groundwork for understanding one of the most important, yet most elusive, components of brain function, namely our ability to selectively attend to one thing out of several, as well as switch attention," Sur said.

Anesthetic drastically diverts the travels of brain waves

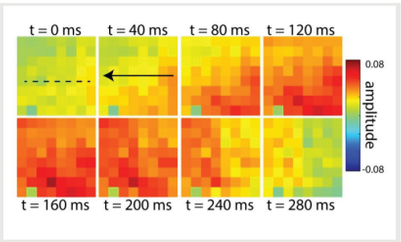
The anesthetic drug propofol substantially alters how different frequencies of brain waves travel across the brain's surface, or cortex, according to a study in the *Journal of Cognitive Neuroscience* by scientists at The Picower Institute.

Conscious brains exhibit a mixture of waves of various frequencies rotating or traveling straight in various directions, but brains under propofol anesthesia became dominated by powerful, very low frequency "delta" waves that roll straight outward in opposite directions instead of slowly rotating around central points as they do during consciousness. Higher frequency "beta" waves, meanwhile, became fewer and more erratically structured, traveling only in directions not dominated by the surging delta waves.

Traveling waves are hypothesized to perform many important functions as they coordinate the activity of brain cells over the areas of the brain they cover. These include reading information out from memory and holding it there while it waits to be used in cognition. They may also aid in perception and act as a means of time keeping in the brain.

The findings therefore illustrate how profoundly anesthesia alters the state of the brain as it induces and maintains unconsciousness, said senior author Earl K. Miller, Picower Professor of Neuroscience.

"The rhythms that we associate with higher cognition are drastically altered by propofol," Miller said. "The beta traveling waves seen during wakefulness are pushed aside, redirected by delta traveling waves that have been altered and made more powerful by the anesthetic. The deltas come through like a bull in a china shop."



Recording of a traveling wave passing under an electrode over time. Warmest colors indicate the peak of the wave.

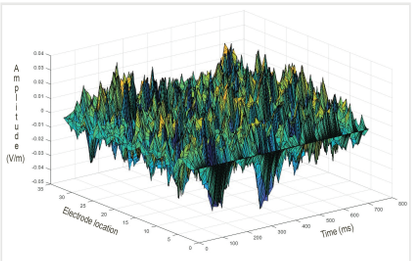
Co-senior author Emery N. Brown said the findings illustrate that there are many ways anesthetic drugs can act on the brain.

"The traveling waves generated by propofol help us appreciate that there are many dynamical phenomena that anesthetics create that can contribute to altered arousal states such as unconsciousness," said Brown, an anesthesiologist at Massachusetts General Hospital and Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience. "It is unreasonable therefore, to think that there is a single mechanism of action for all anesthetics."

Sayak Bhattacharya, a postdoctoral Picower Fellow in Miller's lab, led the study.

Neurons are fickle. Electric fields are more reliable for information.

The most consistent and reliable representation of information the brain is holding in mind is not the electrical activity of the individual neurons involved but the overall electric field they collectively produce, an MIT study suggests.



Estimated amplitude of a neural electric field at each electrode over an 800 millisecond time frame.
Image by Dimitris Pinotsis.

Whenever neuroscientists have looked at how brains represent information in working memory, they've found that from one trial to the next, even when repeating the same task, the participation and activity of individual cells varies (a phenomenon called "representational drift").

In a new study in *NeuroImage*, scientists at The Picower Institute and the University of London found that regardless of which specific neurons were involved, the overall electric field they generated provided a stable and consistent signal of the information animals were tasked to remember.

In a sense, once established, the field imposes itself on the neurons like the conductor of an orchestra in which each neuron is a single musician, said Dimitris Pinotsis, the study's lead and corresponding author. Even if the musicians change, the conductor still coordinates whomever is in the chairs to produce the same result.

"This ensures that the brain can still function even if some neurons die," said Pinotsis, an associate professor at University of London and a research affiliate in The Picower Institute at MIT. "The field ensures the same output of the ensemble of neurons is achieved even after individual parts change. The brain does not need individual neurons, just the conductor, the electric field, to be the same."

Co-author Earl K. Miller, Picower Professor of Neuroscience, said electric fields may therefore offer the brain a level of information representation and integration that is more abstract than the level of individual details encoded by single neurons or circuits.

"The brain can employ this mechanism to operate on a more holistic level even as details drift," he said.

Aging Brain Initiative seeds 5 research projects

Neurodegenerative diseases are defined by an increasingly widespread and debilitating death of nervous system cells, but they also share other grim characteristics: Their cause is rarely discernible and they have all eluded cures. To spur fresh, promising approaches and to encourage new experts and expertise to join the field, MIT's Aging Brain Initiative (ABI) awarded five seed grants after a competition among labs across the Institute.

The ABI, directed by Picower Professor Li-Huei Tsai, promotes research, symposia and related activities to advance fundamental insights that can lead to clinical progress against neurodegenerative conditions, such as Alzheimer's disease, with an age-related onset. With an emphasis on spurring research at an early stage before it is established enough to earn more traditional funding, the ABI derives support from philanthropic gifts.

Major support for the seed grants, which provide each lab with $100,000, came from generous gifts by David Emmes SM '76; Kathleen SM '77, PhD '86 and Miguel Octavio; the Estate of Margaret A. Ridge-Pappis, wife of the late James Pappis ScD '59; the Marc Haas Foundation; and the family of former MIT President Paul Gray '54, SM '55, ScD '60, with additional funding from many annual fund donors to the Aging Brain Initiative Fund.

A team led by Associate Professor Thomas Heldt, proposes to use artificial intelligence tools to bring dementia diagnostics based on eye movements during cognitive tasks to everyday consumer electronics such as smartphones and tablets.

Institute Professor Ann Graybiel's lab will test the hypothesis that mutations on a specific gene may lead to the early emergence of Alzheimer's disease pathology in a brain region called the striatum.

A team led by Associate Professor Gloria Choi will track a potential source of immune inflammation in Alzheimer's disease by determining whether the brain's meninges, which envelop the brain, becomes a means for immune cells activated by gut bacteria to circulate near the brain where they may release signaling molecules that promote Alzheimer's pathology.

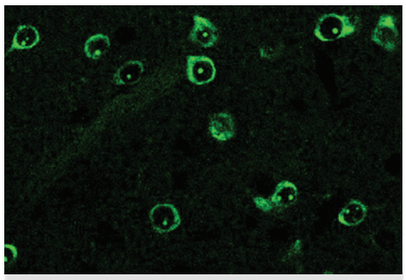
A collaboration led by Singapore Professor Peter Dedon will explore whether Alzheimer's pathology is driven by dysregulation of transfer RNAs (tRNAs) and the dozens of natural tRNA modifications in the epitranscriptome, which play a key role in the process by which proteins are assembled based on genetic instructions.

And with her seed grant, d'Arbeloff Assistant Professor Ritu Raman is launching an investigation of possible disruption of intercellular messages in amyotrophic lateral sclerosis (ALS), a terminal condition in which motor neuron degeneration causes loss of muscle control.

NIH award to help unearth the roots of **Huntington's** pathology

The mystery of understanding and treating Huntington's disease (HD), a fatal neurodegenerative disorder, is not in the cause. Instead what confounds scientists is how and when the well-known mutation of the Huntingtin gene sets off cascades of destruction deep within the brain.

To better understand disease emergence and therefore find earlier targets for therapeutic intervention, Associate Professor Myriam Heiman will use a major new award from the National Institutes of Health to use highly sensitive measures of gene expression early in the disease progression in mouse models.



Spiny projection neurons labeled for analysis. *Image courtesy Heiman Lab.*

In 2020, Heiman's lab published two pioneering studies revealing important potential mechanisms of HD progression, which especially punishes cells called spiny projection neurons (SPNs) in a brain region called the striatum.

One study revealed how certain genes that regulate the expression of others seemed crucial for promoting survival in the cells. The other investigation showed that a major problem is that RNA leaks out of the cells' mitochondria, and becomes misinterpreted as an "invader," setting off a destructive innate immune response.

But the studies, which were conducted in six-month-old mice, also raised new questions including when do such fateful cascades of immune activation and gene expression dysregulation begin, and what sets them off. Supported by a prestigious new eight-year Research Program Award (R35) grant, Heiman will probe for the roots of such problems, and seek to discover any new ones, in more and younger mice – at substantially earlier time points when pathology may be just beginning to develop. "In mice we can look at the earliest stages of disease progression," said Heiman. "Going earlier in phenotypic time and using very sensitive techniques can help us look at what's initiating this cascade of negative events."

"I'm truly honored to have received this award," she said. "I'm delighted that this will broadly support our HD work going forward."

Li-Huei Tsai and Mriganka Sur congratulate Emery N. Brown at a gathering in his honor.

Brown wins share of 2022 Gruber Neuroscience Prize

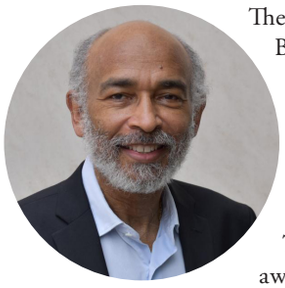
The Gruber Foundation announced in May that **Emery N. Brown**, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience, has won the 2022 Gruber Neuroscience Prize along with three other researchers.

The Foundation said it honored the recipients for their seminal contributions to the fields of computational and theoretical neuroscience. As datasets have grown ever larger and more complex, these fields have increasingly helped scientists unravel the mysteries of the how the brain functions in both health and disease. The prize, which includes a total $500,000 award, will be presented in San Diego, California, on Nov. 13 at the annual meeting of the Society for Neuroscience.

Brown, who is a neuroscientist, statistician and anesthesiologist, said: "It is a pleasant surprise and tremendous honor to be named a co-recipient of the 2022 Gruber Prize in Neuroscience. I am especially honored to share this award with three luminaries in computational and theoretical neuroscience."

Brown's achievements include a novel algorithm to decode the position of an animal based on the activity of just 30 place cells in the brain. He has advanced methods for analyzing numerous other neuroscience datasets, notably including EEG recordings made during anesthesia. He is now working to develop a new research center at MIT and Massachusetts General Hospital to further integrate anesthesiology with neuroscience.

Brown, Sur honored by AIMBE



The American Institute for Medical and Biological Engineering recently honored Picower Institute investigators **Emery N. Brown**, Edward Hood Taplin Professor, and **Mriganka Sur**, Newton Professor, in recognition of their contributions.

The national organization awarded Brown its highest honor, the Pierre Galletti Award, for "significant contributions to neuroscience data analysis and for characterizing the neurophysiology of anesthesia-induced unconsciousness and demonstrating how it can be reliably monitored in real time using electroencephalogram recordings."

Sur earned election to AIMBE's 2022 class of fellows for developing technologies to image brain cells, synapses and circuits and applying them innovatively to elucidate neuronal plasticity and computations.

AIMBE

The AIMBE College of Fellows comprises the top two percent of medical and biological engineers in the country.

Gloria Choi earns tenure

This spring MIT's Executive Committee approved **Gloria Choi**'s promotion to Associate Professor with Tenure, a new rank that took effect July 1. "Since joining the Department of Brain and Cognitive Sciences (BCS) in 2013, Gloria has rapidly established herself as a world leader in neuroimmunology, making remarkable discoveries about the interactions between neural and immunological systems, and providing important insight into how these interactions become consequential for brain development, function, and behavior," BCS Department Head Michale Fee said in announcing the decision. "Her work represents the epitome of a rigorous mechanistic approach to fundamental scientific questions, with tremendous translational potential."

Sara Prescott named affiliate member

The Picower Institute is proud to welcome **Sara Prescott** as an affiliate faculty member. Prescott, assistant professor of biology, investigates how sensory inputs from within the body control mammalian physiology and behavior.

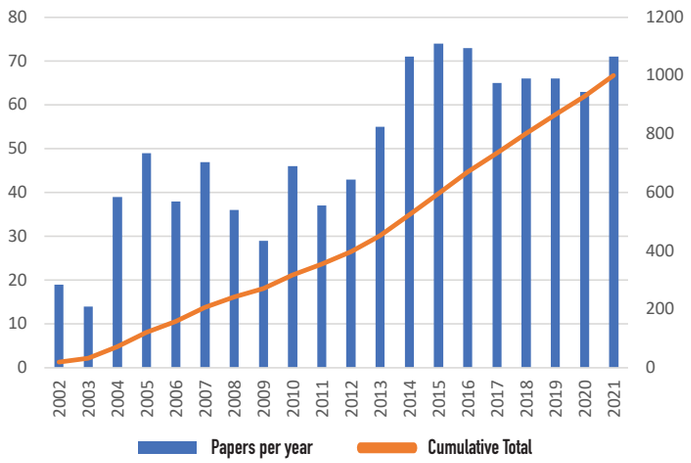
For example, what mechanisms elicit a reflexive cough? Prescott considers the critical questions of how airway insults are detected, encoded, and adapted to mammalian airways with the ultimate goal of providing new ways to treat autonomic dysfunction.

The Picower Institute
BY THE NUMBERS

PEOPLE

Total current community: 265
Faculty: 13 core + 4 affiliates
PhD research staff: 79
Other research staff: 57
Graduate students: 54
Undergraduate students: 27
Administrative & support staff: 31
Alumni: About 500 *(and counting)...*

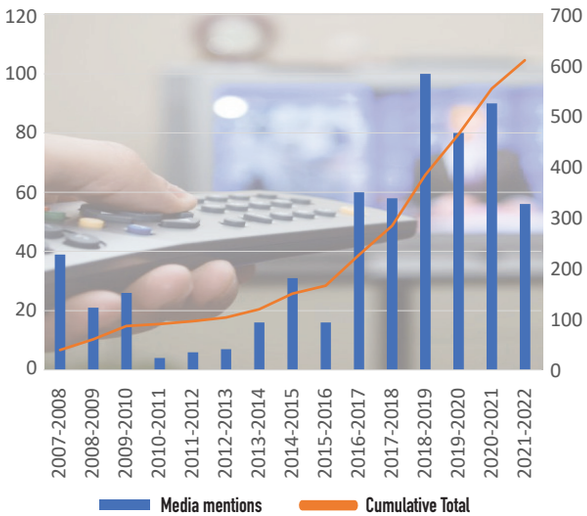
FACULTY RESEARCH PUBLICATIONS



EVENT ATTENDANCE

In the 5 years spanning 2017–2021, The Picower Institute, Aging Brain Initiative, and Alana Down Syndrome Center symposia reached 7,697 registrants from 58 countries on all 6 populated continents.

SIGNIFICANT NEWS MEDIA MENTIONS *2007-2022*



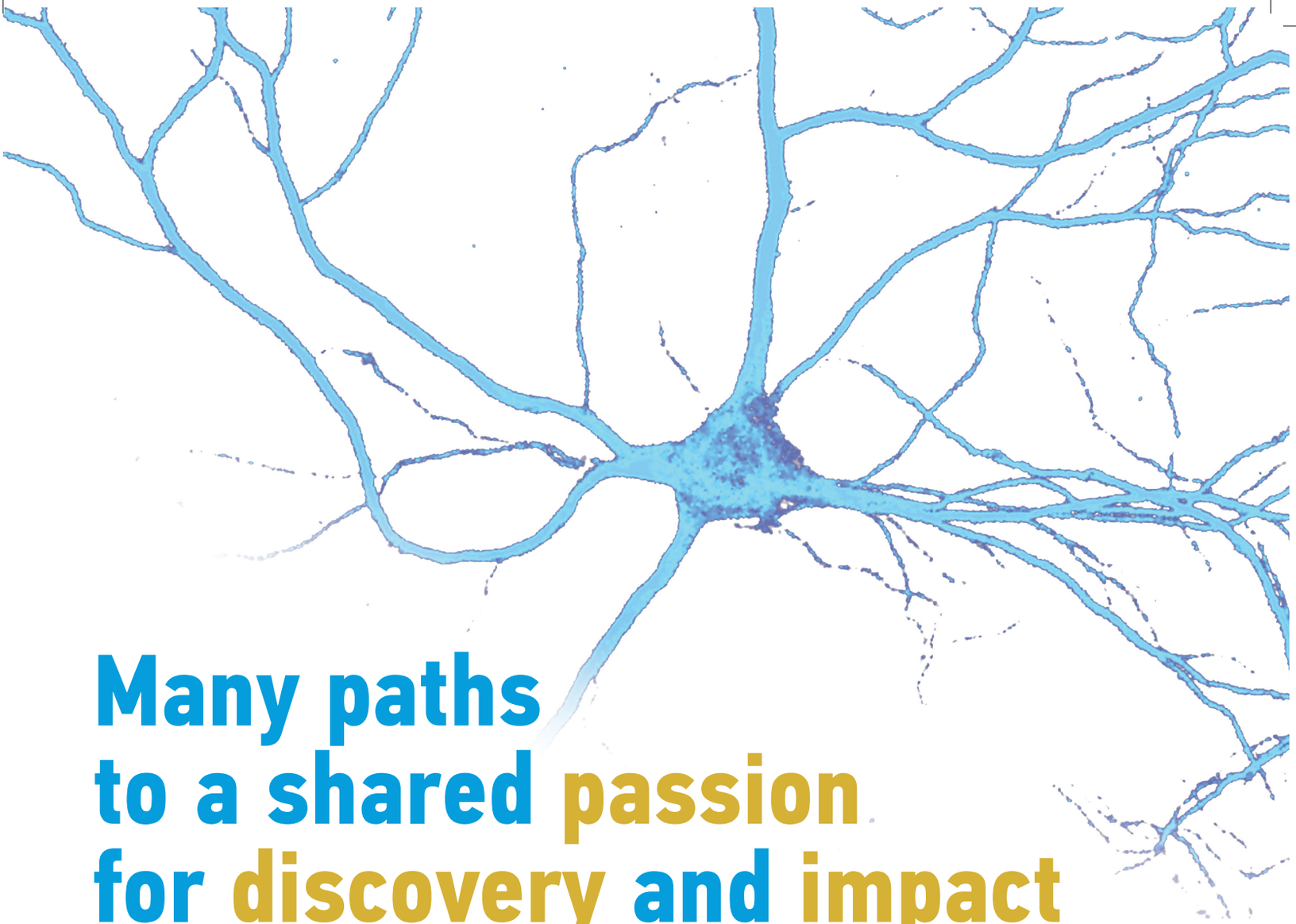
PATENT ACTIVITY

80 patents granted worldwide since 2002 to Picower Institute investigators based on disclosures to MIT's Technology Licensing Office.

SOCIAL MEDIA AUDIENCE

as of June 2022

Twitter: 7,628 ***Instagram: 2,135***
YouTube: 955 ***LinkedIn: 631***

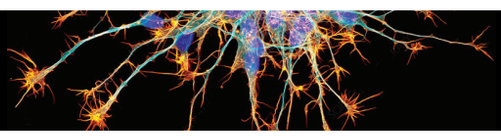


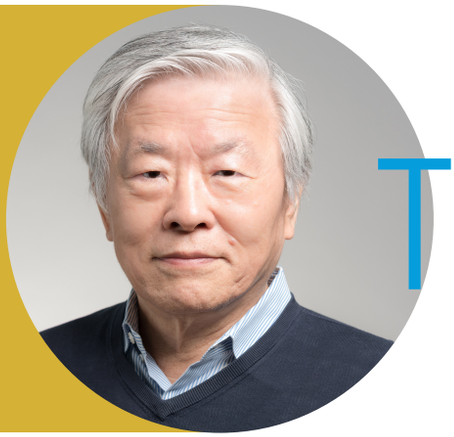
Many paths to a shared passion for discovery and impact

Members of The Picower Institute faculty have each arrived by a different route and followed individual, but often intersecting, paths. The diversity of their backgrounds, questions, approaches, and findings is a signature strength of the Institute.

Yet they are united as well by a calling to advance our understanding of the brain in health and disease. Their labs have accomplished much individually and collectively, and after 20 years are continuing to excel into the Institute's third decade. Here are their stories.

And to learn more about their labs' discoveries, visit picower.mit.edu/research/discoveries.





Susumu TONEGAWA

"I didn't think about ... 'Could it be too risky?... That never occurred to me. I just followed my curiosity and instinct."

Don't shy away from following your curiosity wherever it leads. Instead, look to the superlative career of Picower Professor Susumu Tonegawa for inspiration.

As a chemistry undergraduate at Kyoto University, Tonegawa learned of an emerging discipline: "molecular biology." He became struck that organisms could be understood not just by observing their anatomy and behavior but also by investigating properties emerging from the DNA, proteins and other biochemicals produced and processed in their cells. But, there was nowhere in Japan he could learn molecular biology so journeyed to UC San Diego for his PhD.

Since then, in worlds as seemingly distinct as phage genetics, immunology and neuroscience, Tonegawa's eagerness to use molecular biology to explore whichever questions intrigued him most has led to historic scientific breakthroughs and the creation of The Picower Institute for Learning and Memory.

"When I decided to become a scientist, my criteria of what to do was whether the scientific problem I got to solve was interesting or not," he said. "Whether I'm curious or not. I didn't think about other things, like it, 'Could it be too risky? Can I really develop my career by venturing into the field I am not familiar with?' That never occurred to me. I just followed my curiosity and instinct."

For instance, when visa issues forced him to leave the U.S. after a brief postdoc period, he landed in an immunology Institute in Basel, Switzerland. As he quickly learned the field he became curious about a major unsolved problem: How the immune system, given a limited set of genetic instructions, can produce whatever antibodies are needed to combat the billions of potential pathogens nature throws at us. Figuring that out in 1976 made him the sole winner of the 1987 Nobel Prize. A committee member described the accomplishment as a "one in 100 years discovery."

MIT hired Tonegawa in 1981 as an immunology professor in its cancer center, but after 10 highly productive years his curiosity shifted to the brain. In 1994 he founded MIT's Center for Learning and Memory and in 2002 worked with then President Chuck Vest to vastly expand the effort with a landmark gift from Barbara and Jeffry Picower, forming The Picower Institute.

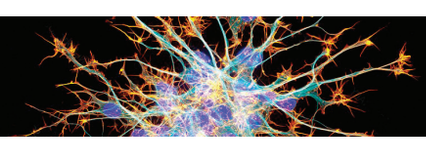
Tonegawa's research brought molecular biology and other advanced genetic tools to the study of memory. In 1992 his lab began identifying genes crucial for memory, demonstrating that knocking them out in hippocampus neurons impeded memory formation and retrieval. In 2012, the Tonegawa lab pinpointed and artificially reactivated an "engram," an ensemble of neurons whose pattern of connectivity physically encodes a specific memory. The lab became so sophisticated with this memory-finding technique they also artificially manipulated memories. For instance, by artificially reactivating the engram of a cage while giving the mouse a little shock in a different enclosure, they could instill an artificial fear of the first cage even though the mouse never actually experienced a shock while physically there.

The Tonegawa lab's many influential papers have also revealed important distinctions between memory storage and recall. In 2015 they found that by weakening engram neurons' ability to synthesize proteins, they could prevent recall of memories but that artificial reactivation of these engrams still enabled recall, demonstrating that their storage was unaffected. The next year, the lab demonstrated that Alzheimer's modeling mice had this property in which recall, but not memory storage, was compromised, suggesting that memory could be recovered. Tonegawa has also led influential findings about how memory is associated with positive and negative emotional valences (and how those associations can be manipulated, for instance to lessen anxiety). The lab has shed new light on how social memory works, how the brain remembers sequences of events, and that memory storage is widely distributed around the brain (see page 3).

Now, the Tonegawa lab is elucidating the neurobiological mechanism underlying knowledge: understandings formed, stored and mobilized broadly and flexibly when we encounter an unfamiliar event. The lab has demonstrated that engrams representing the common components of multiple experiences play a crucial role for this purpose.

Tonegawa said, "The neurobiology of knowledge has been poorly known, and we have discovered an entirely new principle."

It's another insight born from Tonegawa's fruitful curiosity.



Matt WILSON

"We create from our experience stories that tell the story of our lives, that make sense in a way that allow us to make decisions in the future.

A neuroscientist and engineer, Matt Wilson seeks to understand intelligence: how it is embodied in the brain and how it could be created in machines. The measure of intelligence, he says, is how well we make sense of the world so that we can adapt and thrive.

"Dealing with complexity and uncertainty and developing behavioral strategies that allow you to succeed is what we think of as genuine intelligence," says Wilson, Sherman Fairchild Professor of Neuroscience.

As a postdoc in the early 1990s his desire to understand how the brain produces intelligent behavior drew him to the University of Arizona lab of Bruce McNaughton where Wilson focused on a region of the brain, the hippocampus, that is crucial both to forming memory and navigating space. In the lab he recorded electrical activity in the neurons of rats as they found their way through mazes. One day after a rat fell asleep, Wilson heard something remarkable over the lab's audio amplifier, which turned the neurons' electrical spiking into audible clicks.

"What I heard when the animal was asleep was what sounded like the recapitulation of their experience," he said. "The brain sounded like the animal was up and running around. But when I turned to look, I saw that the animal was actually asleep and was in the process of dreaming."

The serendipitous discovery helped to confirm hypotheses that sleep plays an important role in memory. When Wilson came to MIT in 1994 to join its fledgling Center for Learning and Memory (now The Picower Institute, of which he is associate director), he continued to study this memory "replay" phenomenon.

In a series of papers, Wilson and lab members have found that replay occurs at different speeds during different phases of sleep. They discovered that the memories are replayed in fragments and sometimes in reverse order. In a paper in 2009, Wilson's lab showed that animals even replay memories during wakeful rest.

The studies reveal something profound about how the brain processes memory of experience, Wilson said. It doesn't just recall memories exactly as they happen. It breaks memories of experience up into meaningful pieces and reconsiders them in different ways to build something greater.

"We create from our experience stories that tell the story of our lives, that make sense in a way that allow us to make decisions in the future," he says.

Not surprisingly, many of these papers have become highly cited by artificial intelligence researchers. In keeping with his long-term interest in AI, Wilson is associate director of MIT's Center for Brains, Minds and Machines.

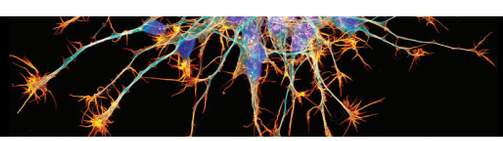
In other studies, Wilson's lab has made measurements in brain areas that converse with the hippocampus, such as the lateral septum, finding that it serves as a crucial hub to integrate spatial information, information about movement, and information about the specific location of rewards. Such a system would seem crucial to serving a primal demand on intelligence: understanding how to get back to a remembered food source.

His lab has also eavesdropped on the conversations—often spoken in the language of brain rhythms—that the hippocampus has with the cortex and the thalamus to better understand how they help to govern behavior. Given the crucial nature of some of these circuits for autism, his lab has contributed to studies of the disorder.

Ever the engineer, Wilson has driven innovations in neural recording methods and hardware including devices called tetrodes that can simultaneously record the activity of hundreds of neurons across multiple brain regions. He and colleagues founded a non-profit called Open ePhys (for electrophysiology) to disseminate such new technologies to the neuroscience community.

In some of his lab's latest work, members are using other innovative technologies to track the emergence of learning as it happens, showing that over the course of training, with periods of sleep, more neurons in the hippocampus become involved in representing spatial contexts, progressively fine tuning mental maps of places.

It's another insight into how the brain enables intelligence.



Earl K. MILLER

"I like solving puzzles, and the brain's the greatest puzzle I know of...It's why we're here. It's why we do what we do. It's how we create everything.

To Picower Professor Earl K. Miller there is no greater puzzle than understanding how the brain produces willful thought.

"I like solving puzzles, and the brain's the greatest puzzle I know of," he said. "It's why we're here. It's why we do what we do. It's how we create everything."

Over more than two decades of research at MIT, the tremendous progress Miller has made has come from helping to discover what makes this particular puzzle special: Unlike in a jigsaw puzzle, the components should not be assumed to have invariant, interlocking places. Instead, his lab has shown, cognition and executive brain function work because the brain is fluid and flexible. Sure the brain has distinguishable regions and cells, but what his lab has helped to show is that it functions less like a machine and more like a dynamic network of networks.

"When I was a graduate student, the dominant thought was that the brain was kind of like clockwork. Every piece of the brain had one function. Every neuron had one function like a gear in a clock, and we could figure out the brain one piece at a time," he said. "But now what's become increasingly clear to us is that anatomy is not destiny in the brain. The connections are possibility. Anatomy in the brain is like the road and highway system. It just says where traffic could go."

The brain has the latitude to use that substrate of possibility however it needs to achieve its goals. Miller's research has helped to explain how that flexibility emerges and how the brain takes advantage of it to produce functions like making predictions, managing information in working memory, sorting things into categories and deciding how to filter and focus its attention.

Miller was a pre-med major at Kent State University, but volunteering in a neuroscience laboratory hooked him on research. Electrophysiology work often involves playing measurements of brain cell electrical activity on an audio amplifier.

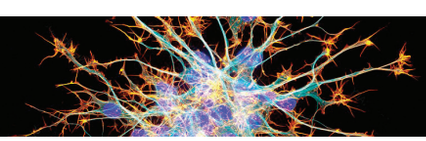
"The first time I did an experiment, I was recording the hippocampus of a rat, and I heard this thunderstorm of all these neurons firing away," he said. "I thought it was the coolest thing I ever heard."

Miller came to MIT in 1995 as one of the first faculty members of the Center for Learning and Memory that ultimately became The Picower Institute. In 2001, in a paper that has become the fifth-most cited in neuroscience, he and Jonathan D. Cohen posited that the prefrontal cortex (PFC) exerts executive control by maintaining activity patterns representing goals and the means to achieve them. The PFC's activity essentially biases other brain structures to serve those goals, by guiding the flow of neural activity along circuits to establish the proper mappings among inputs, internal states, and outputs needed to perform a conscious task.

In a body of work spanning more than a decade, culminating in a 2013 paper with Stefano Fusi, Miller showed that PFC neurons are not locked into specific single roles. Instead they can participate in multiple circuits and to encode a variety of information. He has also produced dozens of studies, based on detailed measurements and often computational modeling, showing that the rhythmic patterns of neural group activity (also known as "brain waves") sculpt and guide the flow of information across the cortex. In his road map metaphor, the waves act like police, directing information "traffic" as needed—for instance keeping attention away from mundane, predictable stimuli so that what's truly new in a scene can gain our focus.

The ability to determine what's predictable is widely believed to be a deficit in autism spectrum disorders. Miller is applying what he's learned to potentially help. A goal of the lab is to develop real-time feedback systems that could augment brain rhythms to improve cognitive control when it falters.

In that way, by solving the puzzle, Miller may be able to help others solve theirs, too.



Mriganka SUR

"I study brain wiring and how it changes during development and during learning in order to enable the brain's extraordinary functions.

During years of undergraduate and graduate study in electrical engineering, Mriganka Sur developed a parallel fascination. Looking past silicon devices, he increasingly became drawn to the brain—a computational machine distinguished by an especially compelling property.

"The brain wires itself, unlike a computer," he said. "Through the information encoded in our genome, together with the information we encounter in the world, that enables the brain to function, to process information. I study brain wiring and how it changes during development and during learning in order to enable the brain's extraordinary functions."

Since he came to MIT in 1986, Sur has explored this dynamic property of self-wiring and change, called "plasticity," in the cerebral cortex, the brain's outer layer that has evolved to provide mammals with advanced cognitive abilities. Over the decades his lab has produced numerous influential studies covering a gamut of scales.

He has studied genes and molecules fundamental to enabling individual neurons to engage in this self-wiring, and characterized dynamic, broader circuits and systems from which learning, memory and behavior arise. Along the way, to enable such deeply probing, but broadly spanning research, his lab has pushed frontiers of brain imaging and advanced research methods from genetic manipulations, to tissue engineering, to computational modeling.

By discovering fundamental mechanisms of brain development, structure and function, his lab has also produced critical insights into how brain rewiring can go awry. A therapy for the neurodevelopmental disorder Rett syndrome, based on one such mechanistic discovery by his lab, is under consideration this year for FDA approval.

Sur made an early mark in his work with research demonstrating that if one cut off input to the auditory thalamus and cortex of a young ferret, that sensory processing part of the brain wouldn't just give up. Instead, it would rewire to become a secondary locus for processing vision.

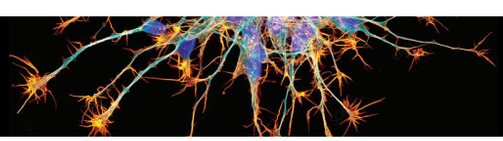
In other studies, Sur's lab has demonstrated how neurons continue to change individual connections and activity throughout life to represent learning. In studies centered on a region where the brain links perception to action, for instance, his lab directly imaged how the responses of cells changed as rules of the experimental task did. In the lab's latest study, his team discovered that the timely and spatially tuned release of the chemical noradrenaline, emanating from a tiny region deep within the brain, drives neural changes supporting learning and memory in the brain's prefrontal cortex (see page 2).

At finer scales, Sur's lab has sought to understand the rules and mechanisms of neural rewiring. In 2018, for example, the lab showed that when a neuron increased the strength of a particular circuit connection, called a synapse, in order to adapt its information processing to changing experience, the protein ARC would mediate a balancing response to weaken other synapses nearby.

And in a series of papers beginning in 2009, his lab discovered that a protein called MECP2 is a critical player in the maturation of synapses via its regulation of another protein called IGF1. Girls with Rett syndrome carry an MECP2 mutation on an X chromosome that reduces levels of IGF1. Sur's lab showed that administering IGF1 peptide corrected many problems in mice modeling the MECP2 mutation. A pharmaceutical company picked up the ball from there and has now completed Phase III clinical trials in patients.

Sur's contributions to the study of autism and autism-like disorders extend way beyond his own lab's work, however. In 2012, after 15 years as head of the Department of Brain and Cognitive Sciences, he took on a new role directing the Simons Center for the Social Brain, a collaborative research community that has seeded numerous autism research projects and funded scores of young scientists across MIT and the Boston area.

Through his own research, and enabling that of others, Sur has substantially advanced our understanding of how the brain wires itself, and how to help it wire better when it doesn't.



Elly NEDIVI

"You just have to think about how you might want to do something and, it may be hard, but it's doable.

In 1998, when Elly Nedivi sought her first faculty job, people at one institution where she interviewed advised her to scale back her agenda, but at MIT Susumu Tonegawa praised the ambition of her research.

Nedivi knew she wanted to go where she could push the limits rather than settle for them. Now the William R. (1964) and Linda R. Young Professor of Neuroscience, she still values that about MIT and The Picower Institute.

"It's an incredibly enabling environment," she said. "Basically, you can do anything. You just have to think about how you might want to do something and, it may be hard, but it's doable."

Nedivi studies how the brain remodels to respond to and incorporate experience (a unique attribute called "plasticity"). Her lab identifies and characterizes genes and proteins whose expression in neurons depend on circuit activity. She has also co-invented advances in microscopy that enable her lab and others to track plasticity in living animals as it happens. In both ways she has revealed a lot.

Nedivi began discovering activity-driven neural proteins as a postdoc at the Weizmann Institute in Israel. At MIT she found that one, which she dubbed CPG2, plays a pivotal role in regulating the sensitivity that neural circuit connections, or synapses, have to the neurotransmitter chemical glutamate. It therefore modulates how excited neurons can become by the input they receive in circuits.

In 2019 her lab showed that CPG2 is also relevant to disease by discovering that people with bipolar disorder often have low levels of CPG2 because of specific mutations in SYNE1, the gene that encodes the protein.

By cloning those variations into rats, the team showed that some reduced the ability of CPG2 to locate in excitatory synapses while others decreased its ability to maintain synaptic receptors for glutamate. The findings thereby identified novel risk gene variations for bipolar and explained how the mutations could undermine circuit function.

"Plasticity is not just a feature of how our brain works," Nedivi said. "It's also kind of a soft spot. It's so fundamental, any mutation in genes that are responsible could result in a behavioral outcome that can be detrimental."

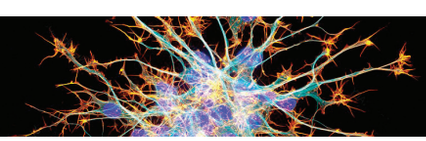
The Nedivi lab's investigation of the protein CPG15 revealed its crucial role in learning and memory. Key cells in the developing brain's cortex must express CPG15 to survive, she found. She also showed that neurons use it to develop their axon and dendrite projections and to stabilize synapses. Mice lacking CPG15 were significantly slower learners. A 2019 study revealed why. In synapses where experience is driving a high level of activity, CPG15 triggers stabilization of that valuable connection, enabling neurons to cement the connections it needs to incorporate experience in its computations.

The study took advantage of innovations in microscopy and synaptic labeling that Nedivi has driven in a 20-year collaboration with MIT Mechanical Engineering Professor Peter So. Together they have developed modifications to traditional two-photon microscopy that enable ongoing imaging of the diverse processes of neural circuit remodeling. They can resolve multiple proteins in different synapses as they appear, disappear, grow or shrink over time as animals' experiences change.

In 2006 Nedivi's lab used its novel microscopy techniques to prove that adult brains are not hardwired as many scientists thought. Instead, they respond to experience by subtly remodeling the sprawling dendrites that their inhibitory neurons project to form circuit connections.

Armed with the unique ability to distinguish inhibitory and excitatory synapses (by labeling and imaging them with distinct colors) Nedivi's lab has also made discoveries about how inhibitory synapses contribute to plasticity. For instance, in 2016 they found that while many excitatory synapses, once established, tend to stick around, inhibitory synapses come and go nearby frequently. That suggests that neurons modulate excitatory circuit connections by adjusting the amount of inhibition around them.

There's a lot we might not know about how our brains respond to experience had Nedivi taken the early advice to scale back her ambitions.



Troy LITTLETON

"...this was the generation of knowledge, the place where no one else in the world knew what you knew.

Menicon Professor Troy Littleton's undergraduate scholarship at Louisiana State University had a work requirement. One of the boxes he checked on a placement form was "research lab," figuring there'd at least be air conditioning. Far more than that, the biology lab he worked in provided lifelong inspiration. The lab studied how fish use their senses of smell and taste to navigate their environment and find food. Littleton was captivated by how the brain transmitted and processed such information.

The experience was eye-opening for Littleton who had wanted to become a doctor, but knew nothing yet of research.

"It was really then that I understood you can actually study the basic biology of how processes work. That gives rise to the knowledge that physicians are going to use to treat patients," he said. "I really had not been exposed to that before, so being in the lab those first couple of years was really amazing. To see that this was the generation of knowledge, the place where no one else in the world knew what you knew."

When Littleton next moved to Baylor College of Medicine for an MD/PhD, he learned new genetic manipulation techniques in fruit flies for studying those biological systems in molecular detail. He focused on the junctions between neurons, called synapses.

"I often think of synapses as radio dials," he said. "They're a way to turn communication up or down, to increase or decrease the amount of information flow between two neurons."

Since he established his own lab at MIT in 2000, Littleton has been reverse engineering that metaphorical radio system, both on the transmitting and receiving sides of the synapse. In flies and humans alike, numerous proteins are involved in building the machinery of these synapses and making them work. Littleton's lab has become among the most prominent and productive in characterizing these proteins and how they enable and control information flow by regulating the supply, release and reception of chemicals called neurotransmitters.

One of the main ways Littleton's lab does this work is by manipulating genes that produce the key proteins to see how synapse structure and function, and other cellular functions involved in neural communication, are affected when the proteins are missing or altered.

For instance, in a pair of 2013 studies, they used genetic manipulations to discover how two proteins, Synaptotagmin and Complexin, control how and when neurotransmitter-containing vesicles fuse to the synaptic membrane for release across the synapse. Complexin acts like a clamp, preventing fusion until synaptotagmin detects an influx of calcium, which is the key signal required for the neuron to release their neurotransmitters.

Many of the lab's discoveries have uncovered mechanisms of "plasticity," which is the neuron's ability to change communication based on alterations to synaptic proteins.

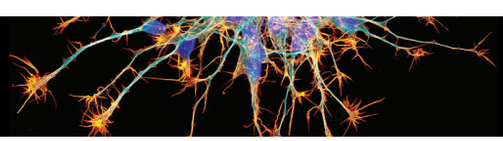
In recent papers, the lab has shown how the presence of a protein called Tomosyn endows some synapses with the ability to hold neurotransmitter in reserve for extra release when needed. Similarly, they've shown how a different version of Synaptotagmin also constrains neurotransmitter availability, thereby giving synapses flexibility to control information by regulating protein expression levels.

And as a result of observing many ways that genetic mutations can break neural communication, the lab has also produced significant insights into the biology of disorders including epilepsy, Huntington's disease, autism and neuropathy.

In screens for genes that affect neural communication, Littleton's lab found a mutation that causes seizures in flies. The gene mutation, which he termed Zydeco, closely models some types of human epilepsies.

Subsequent studies by the lab revealed that it disrupts the way that neural helper cells known as glia regulate extracellular ions, and therefore electric current, around neurons. The research revealed a potential target for addressing epilepsy that doesn't require treating neurons directly.

These studies and others are perfect examples of what Littleton realized in those early days at LSU. Through fundamental research he could generate a solid foundation of knowledge that can inform science and medicine alike.



Mark BEAR

In multiple ways, Bear's childhood inspiration has become a source of hope for addressing childhood brain health.

Through the eyes of a child, the shooting of President John F. Kennedy piqued an enduring curiosity.

"Shortly after the shooting, before it was clear he would not live, there was much speculation on TV of what functions would be impaired by damage to the brain," said Picower Professor Mark F. Bear. "As a 6-year-old, I was amazed. I still am."

Bear's fascination with the brain has matured, but never wavered. In graduate school at Brown University, he drew inspiration from famous experiments showing that temporarily occluding an eye of a developing kitten shifted connections and computational resources in the cat's visual cortex away from the hindered eye and toward the unclosed one. Bear's eagerness to help explain how experience so profoundly shapes the brain has led to him to become a leading authority whose discoveries have produced promising therapies for autism and vision disorders.

The cat experiments modeled amblyopia, in which occlusions such as cataracts degrade the eye's connections in the brain. Treatment involves fixing the original occlusion and patching the "good" eye to force use of the "weak" one. But when Bear was a postdoc, the field's theory of how the brain changes circuit connections, called "plasticity," was insufficient to explain why amblyopia occurred, or why patching helped.

When Bear established his first lab back at Brown, he collaborated with colleagues who theorized how synapses weaken when exposed to weak input, such as that provided by an occluded eye. In the early to mid-1990s Bear's lab discovered the mechanism: a molecular process called "long-term depression" (LTD).

In 2003 Bear moved to MIT. "I really felt that MIT had reached an inflection point in the brain sciences with the creation of The Picower Institute," he said. "Susumu had brought together scientists from different backgrounds that were united in their interests in brain plasticity, learning and memory."

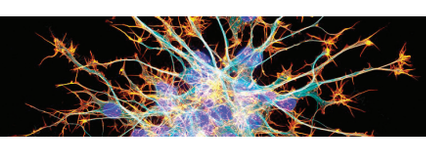
Bear's MIT lab continued to investigate amblyopia, ultimately finding a way to radically improve treatment. While LTD explained the condition, another part of his colleagues' theory predicted why patching works.

When overall activity is reduced, the threshold of input that would strengthen or weaken a synapse shifts lower, so that activity from the weaker eye becomes enough to strengthen it. Bear recognized that if activity were temporarily shut off completely, then the threshold could be lowered so much that the weak eye, upon the resumption of activity, would rebound strongly, even in adults. In papers in 2016 and 2021 his lab showed that the idea works in mice and cats: Temporarily anesthetizing a retina leads to a strong rebound in the brain's response to that eye when the anesthetic wears off.

Another of Bear's fundamental findings has produced a similarly promising therapeutic approach for Fragile X syndrome, a genetically caused form of intellectual disability and autism. In 2002, Bear's lab discovered that the protein that becomes compromised in Fragile X syndrome, FMRP, acts like a brake on a molecular mechanism of LTD driven by a neural receptor called mGluR5. He realized that a possible treatment for Fragile X would be to replace the lost brake by inhibiting mGluR5 with a drug. In studies including in 2007, Bear's lab showed that the idea worked in mice and the therapy entered clinical trials in later years. The candidate drug barely missed its goal, and Bear's lab has more recently shown that was likely due to drug tolerance, which can be avoided. He has also worked with MIT colleagues to develop a new compound that doesn't build up tolerance effects.

In yet a third line of research, Bear's lab has discovered new capabilities of the visual cortex. He has found that it can learn to predict sequences and to recognize repeated images as familiar, a property called "visual recognition memory." Because people with autism have difficulty habituating to frequent stimuli, he is working with clinicians at Boston Children's Hospital to determine whether tests of visual recognition memory could be an early diagnostic.

In multiple ways, Bear's childhood inspiration has become a source of hope for addressing childhood brain health.



Li-Huei TSAI

Tsai saw dementia affect her grandmother.

> *I always remember her and think that whatever I do now, I may be able to help people just like her.*

Li-Huei Tsai didn't set out to direct a top brain research institute or a highly accomplished lab focused on Alzheimer's disease.

But when one combines a passion for discovery and a desire to make an impact with personal inspiration and an openness to pursue new results to whichever unexpected places they lead, that can be a path to leadership.

Starting her faculty career at Harvard, Tsai studied cancer biology. She discovered an enzyme, Cdk5, that turned out to be especially active in the brain during development. She soon discovered that when it became misregulated in adult lab mice it could cause serious neurodegeneration and pathology similar to Alzheimer's.

"I started to be exposed to the Alzheimer's disease literature and community and I realized if I work on the disease, I can make a lot of contributions," she said.

Tsai knew the importance and urgency. Growing up near Taipei, Tsai saw dementia affect her grandmother.

"I always remember her and think that whatever I do now, I may be able to help people just like her," Tsai said.

Tsai joined The Picower Institute in 2006, excited by its focus on memory and its embrace of a wide variety of research methods and approaches. As her lab continued to work with Cdk5 mice and other Alzheimer's disease models, she and her lab members made several discoveries that surprised the field, but ultimately became very influential.

Her lab found that the enzyme HDAC2 can become overly active in Alzheimer's disease, locking down gene expression for proteins that neurons need for memory recall. They showed that chemically inhibiting HDAC2 restored recall. Her lab also found that quick gene expression for memory storage requires neurons to break both strands of their DNA. Neurons can repair these breaks, but aging brains with flagging levels of HDAC1 experience a harmful accumulation of damage. The deficit is evident in postmortem brain samples from Alzheimer's patients, but her lab has shown that drugs that enhance HDAC1 aid repair and improve cognition in mice.

In 2016, Tsai's lab made an especially unconventional discovery. Led by graduate student Hunter Iaccarino, they found that increasing the power of 40Hz brain waves significantly reduced Alzheimer's pathology in multiple mouse models. They showed that this power boost could be entrained through the senses—just by flashing light at 40Hz. Subsequent studies showed that 40Hz sound worked, too, and that the two work best together. Alzheimer's mice exposed to 40Hz stimulation experienced less neuron death and showed improved memory. Testing in humans is still in early stages, but suggest that 40Hz sensory stimulation is safe, can preserve brain volume and sustain memory. An MIT spin-off company is now starting Phase III clinical trials.

"These very unexpected findings have been quite a journey," she said.

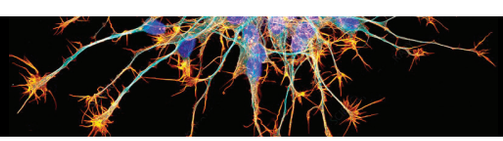
Tsai's lab has also taken advantage of two new technologies to broaden its research further. With MIT artificial intelligence experts, the lab has performed sweeping analyses of gene expression data to understand how it differs between healthy people and those with Alzheimer's. They also take skin cells donated by patients and reprogram them to become stem cells. Those can then be cultured into brain cells and tissues including neurons and even blood vessels. Together these technologies allow the lab to identify consequential genes and then test their implications in complex human tissue models. The lab can also test the effects of candidate therapies.

Tsai's collaborations have helped to spur broader research efforts at MIT: The Aging Brain Initiative and the Alana Down Syndrome Center. People with Down syndrome have a very elevated risk of Alzheimer's disease.

She became director of The Picower Institute in 2009. As much as her lab and the broader field have discovered, Tsai knows there is much more to do. Alzheimer's remains terminal, untreatable and deeply mysterious.

"It's become clear that not all Alzheimer's is the same for patients," she said. "We think there are different kinds of Alzheimer's caused by different etiologies and that different kinds of interventions probably are needed."

With an open-minded and innovative research program, Tsai's lab is indeed making a rich variety of contributions.



Myriam HEIMAN

"I feel that we're really on the cusp of uncovering therapeutic targets that will be game changers.

Somewhere amid the damage in a brain succumbing to a neurodegenerative disease are the critical clues explaining what has gone wrong, and therefore the key to preventing it in the future. Associate Professor Myriam Heiman likens efforts to understand what makes brain cells vulnerable to diseases such as Huntington's, Parkinson's and Alzheimer's to police detective work.

The task is complex. The brain's billions of cells come in thousands of types. The properties of each are governed by the unique pattern of how the cells express more than 20,000 genes. Even in Huntington's disease, where scientists have identified the exact mutation that causes specific neurons in a particular brain region to die, they still can't say for sure how it proves lethal to those cells, why patients ultimately cannot survive, and how to change that fate.

"We are a bit like detectives looking at the crime scene and we find these clues of genes that are turned on or off," she said of her lab. "And we try to make inferences and draw correlations and say, 'Likely the culprit here was X or Y or Z'."

Early in her still young career, Heiman realized that if she was going to find the answers—and she has made significant inroads—she'd need innovative ways to penetrate the extraordinary complexity of the brain.

As a postdoc at the Rockefeller University, Heiman helped invent TRAP, a method of isolating the gene expression of any specific type of cell by tracking the messenger RNA it translates from its genome. The technique helps her and others understand what makes each kind of neuron different and how they respond to disease. When it came time to establish her own lab in 2011, she chose MIT.

"I never envisioned myself working at a primarily engineering school because my training was at biomedical research institutions, Johns Hopkins and the Rockefeller University, which are behemoths in biomedical research," she said. "But I started to realize that computational approaches, bioengineering approaches, genomic approaches, and the interface of these are what will enable the next round of discoveries.

The Picower Institute is an intersectional point for expertise in these areas. That's what makes it such fertile ground for discovery."

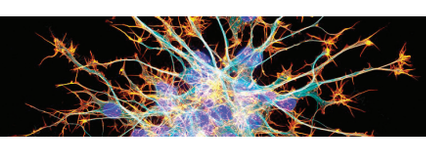
Here she has achieved important "firsts." Her lab invented a new technique for testing out how much each gene matters for neuronal survival, both in general and amid disease. In 2020 this method in mouse models enabled Heiman's team to discover a gene especially crucial for cells afflicted with Huntington's mutations and showed that overexpressing it improved disease symptoms. Next her lab hopes to apply the technique to find genes that could be augmented in Parkinson's disease.

And by combining TRAP with another RNA screening technique, Heiman's lab in 2020 produced the most comprehensive look yet at how cells in both mouse and human brains respond to the mutation that causes Huntington's disease. The study revealed that in the disease mitochondrial RNAs leak out, triggering a destructive immune response that might also be targeted therapeutically.

To confront the "big data" problem posed by all this genomic data, Heiman collaborates with computer scientists. With colleagues at the Sorbonne in France she used new computational methods to find that another contributor to cellular demise in Huntington's disease is a breakdown in systems meant to maintain cell health. And earlier this year working with MIT computational biologist Manolis Kellis her lab unveiled the first atlas of cell types that comprise the human brain vasculature, revealing how Huntington's disease degrades the brain's circulatory system.

With such tools and advances, which she is now also applying to study substance use disorder and schizophrenia, Heiman finds reasons for optimism.

"I like to tell the students in my classes every year that 'Within our lifetime, we may have cures for these incurable diseases'," she said. "And every year I say that, but I believe it more and more now. I feel that we're really on the cusp of uncovering therapeutic targets that will be game changers."



Kwanghun CHUNG

"What if we could look in an unbiased way? We could find key factors involved in many neurological disorders that we may have been missing."

The brain is a whole system—an integrated network of networks—but neuroscientists until about a decade ago had no clear way to look at its billions of cells and proteins intact and in situ, even in a brain as small as a mouse's. But beginning as a postdoc at Stanford and continuing when he launched his MIT lab in 2013, Associate Professor Kwanghun Chung has helped to lead a revolution in tissue processing that has changed how neuroscientists can look at and understand the structure and function of the brain at every scale. Even the huge human one.

The Chung Lab's many chemical engineering technologies can efficiently clear, enlarge, preserve, and rapidly label whole brain samples to highlight virtually any cells or proteins of interest, for instance when comparing brains modeling a neurological disease with healthy controls. Moreover, his interdisciplinary team has developed software tools to automate analysis, extracting discoveries from the enormous amount of data that comes from being able to image whole samples.

"Our goal is to develop rapid, cost-effective and holistic 3D phenotyping and imaging techniques for neuroscience research," Chung said.

"Phenotyping" means characterizing how a brain has turned out based on nature and nurture. For instance, Alzheimer's brains are riddled with protein plaques and tangles and show dramatic deterioration. Picower Professor Li-Huei Tsai has worked with Chung and his technologies to show how Alzheimer's disease progresses in the brain and to examine the effects of the potential treatments her lab is developing.

Notably, because it enables studies of whole, intact brains, researchers don't have to decide to study just one region or another. That means their hypotheses and the extent of their inquiries can be unconstrained.

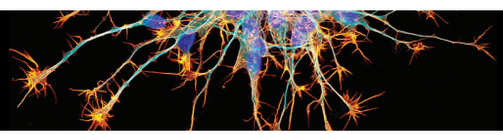
"Our approach is OK, what if we could see everything?" Chung said. "Take a holistic approach instead of a reductionist approach. What if we could look in an unbiased way? We could find key factors involved in many neurological disorders that we may have been missing."

Chung collaborates and shares his technologies widely. Earlier this year Chung's lab published a paper with that of Picower Professor Susumu Tonegawa in which the scientists showed that a memory is encoded by cells in regions all over the brain – including in many areas neuroscientists didn't know about before (see p. 3). In other research his lab has collaborated with Mriganka Sur, Newton Professor of Neuroscience at MIT, and Paola Arlotta, a neuroscientist at Harvard, to trace differences in brain development amid autism-related genetic backgrounds.

In 2020 Chung's lab combined many of his technologies into one streamlined system for analyzing brain organoids, also known as mini-brains. These are 3D tissue cultures of thousands of human brain cells that scientists can grow in the lab to observe early stages of development, disease pathology, and to test drugs. Chung's system, called SCOUT, makes these cultures more useful by not only clarifying, preserving, enlarging, and labeling them, but also by applying machine learning-powered analysis to make rigorous quantitative comparisons of hundreds of different properties. The analyses can even factor out the natural variance among how organoids grow so that researchers can pinpoint the differences made by the variable they are studying. For instance, Chung and MIT colleague Lee Gehrke were able to make novel findings about how Zika virus infection affects organoid development.

Now Chung leads a collaboration that aims to produce an unprecedentedly informative atlas of the human brain. Working with whole brain samples donated posthumously by patients at Massachusetts General Hospital, his team is systematically scanning the brains at sub-cellular resolution and yet across their entire anatomy as well. Chung has likened this to the way Google Maps lets one seamlessly zoom down to the level of individual cars and houses, or out to the whole Earth. By imaging not only the anatomy of cells, but also the distribution of key proteins, the project will reveal not only how the brain is built, but also much about how it functions.

Such a comprehensive view of the brain would have been unthinkable a decade ago.



Emery N. BROWN

"That's not only a deep question, it's an important question... making anesthesia safer, making it better, and coming up with new ways of doing it.

A leading expert in each of three distinct fields—statistics, neuroscience, and anesthesiology—Emery N. Brown, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience, is championing a unique integration of all three to improve care for patients.

Tens of millions of people worldwide undergo general anesthesia every year, a testament to the field's empirical success. But anesthesiology hasn't developed a theoretical foundation based in the brain. In the operating room anesthesiologists typically monitor consciousness via indirect indicators such as movement and changes in heart rate and blood pressure. Brown is emphasizing analytical rigor and neuroscience knowledge in anesthesiology, hoping to drive innovations analogous to the progress cancer treatment made based on the development of its biological foundation.

"Anesthesiology doesn't have that core, basic science from neuroscience that it can build the future on," said Brown, who practices at Massachusetts General Hospital. "That's not only a deep question, it's an important question. And in getting a good solution to it, there are immediate benefits. In particular, making anesthesia safer, making it better and coming up with new ways of doing it."

It's a clear and compelling vision, but Brown acknowledges that he didn't formulate it right from the start of his career, when he earned his MD in 1987 and his PhD in statistics in 1988 at Harvard.

What first attracted him to neuroscience (and ultimately to The Picower Institute in 2015) was not its potential to inform anesthesiology, but rather the signal processing challenges raised by the explosion of data coming from labs.

For example, in the 1990s he collaborated with Matt Wilson, who was recording electrical activity in the hippocampus neurons of rats navigating mazes. Brown developed new methods to analyze the data. Brown's statistical acumen has helped to improve analysis of functional MRI measurements, developed algorithms for brain-controlled prosthetics, pinpointed the sources of EEG and MEG brain wave measurements, measured circadian rhythms and even improved analyses of variability in heart beats.

"The more I worked with Matt and other neuroscientists talking about data analysis questions, I realized that the paradigms that they were using to study other questions, like Matt was studying learning and memory, could be brought to bear to study how the brain works under anesthesia," Brown said.

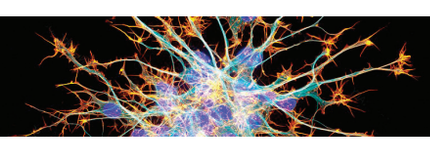
Brown's analyses of EEG readings from patients and animals under general anesthesia have yielded major advances in understanding how various anesthetics uniquely act on the brain and how that can vary in different patients, for instance depending on age. In recent papers with Earl K. Miller, for instance, Brown has shown that anesthetic drugs radically disrupt brain wave activity, cutting off the typical means of communication that sustain consciousness.

His analyses have also produced readily detectable signatures for precisely tracking unconsciousness based directly on brain activity. By including EEG readings as he monitors his patients in the OR, Brown is able to carefully adjust drug dosing so that he gives patients exactly what they need without overdosing them. That can reduce post-operative side effects such as delirium. And by studying how different anesthetic drugs affect the body's subconscious damage sensing system—called nociception—he can better mix and match anesthetics to manage intra-operative and post-operative pain, potentially reducing the need for opioids.

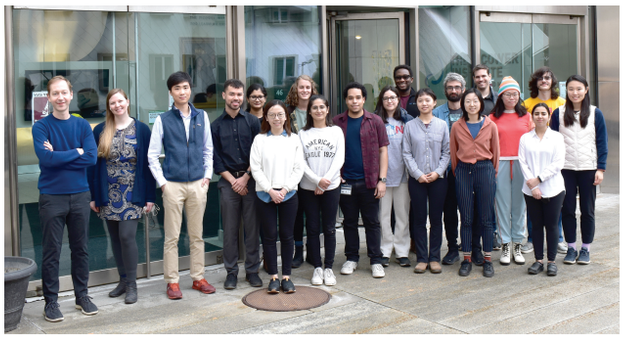
And for all the ways that making the brain the focus of anesthesiology can improve clinical care, there may be just as many ways that it can improve clinical neuroscience, Brown adds.

"Focusing on how you turn the brain 'on' and 'off' for anesthesia purposes immediately leads you into questions like how could you turn it 'on' better so that you could treat depression? How could you turn it 'off 'better so you could sleep better? How could you turn it 'on' better so maybe you could wake someone up from coma?"

With questions like these in mind, Brown is now working with MIT and MGH to develop a major new research program: the Brain Arousal State Control Innovation Center. It would be a center that puts the brain at the center of anesthesiology and disorders of arousal control.



Steve FLAVELL



"You have a sense at that moment that you're about to set yourself on a path…I knew that it was what I had to do."

Steve Flavell recognized this next choice would determine his life's path for years to come. Having completed his PhD at Harvard, he now had to decide upon his postdoctoral research—the last step before setting up his own lab. After research and deliberation, he realized his choice was clear—a transparent, millimeter-long worm with 302 neurons.

"You have a sense at that moment that you're about to set yourself on a path," said Flavell, Lister Brothers Career Development Associate Professor. "I started reading and thinking about the way that a simple system, like *C. elegans*, could be studied in order to really give rise to an understanding of how neural circuits generate behavior … and then I couldn't stop thinking about it, I knew that it was what I had to do."

So why the *C. elegans* worm? Because unlike any other animal it is simple enough to study at every scale that neuroscience must encompass: genes, proteins, cells, circuits, systems and behavior. Moreover, its nervous system fundamentally works like that of more complex animals including humans. So the discoveries Flavell's lab has been making ever since he came to MIT in 2016 have advanced what neuroscientists know about how brains sense their environment, integrate information into internal states like hunger, and generate appropriate behaviors. They also could illuminate how, if such fundamental mechanisms become altered, behavior can become errant, as in psychiatric disease.

All the connections among *C. elegans's* neurons were mapped years ago, making it the only animal where we have a full blueprint of the brain. With this resource, Flavell's lab can ask questions about how the nervous system functions. How do brain circuits sustain and then flexibly change behavior? To ask these questions, Flavell's lab has invented new microscope systems that can constantly track the activity of every neuron and track every behavior. The scientists can also manipulate the worm's genes and circuits artificially to see what difference strategic perturbations make. Every component is accessible for study.

In 2019, the lab uncovered a surprising linkage between humans and worms when they discovered what makes a worm slow down when it finds a patch of the bacteria it eats. It turns out that a neuron called NSM reaches into its gut to deploy sensors called ion channels to detect when bacteria are being eaten. That signals a flood of serotonin release in the worm's brain that slows the worm down so it doesn't miss the meal. The ion channels they discovered are also expressed in human intestines, so the study shed new light on the connection between our guts and brains, too.

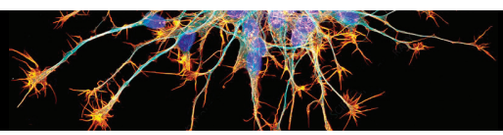
Last year Flavell built on that to discover an elegant circuit in the worm that integrates multiple sensory inputs to allow the worm to decide between long-lasting behavioral states: when to forage for food and when to stop to graze.

The decision starts when the neuron AIA detects the smell of food. If NSM confirms the worm is eating, it inhibits movement with serotonin. But if food is smelled and no eating is happening, other neurons inhibit NSM with a different neurotransmitter, allowing foraging toward the smell to proceed.

The lab has also revealed how dopamine allows neural circuits to coordinate multiple motor behaviors, such as when the worm cruises through a food-filled area to lay its eggs like a farmer seeding crops in fertile soil. When a neuron senses the presence of food and integrates that with information incoming from other neurons about movement, it releases dopamine to override the release of GABA that otherwise inhibits egg laying.

As Flavell teases out fundamental mechanisms of how neural circuits and neurotransmitters drive flexible behavior, he is also considering the clinical implications these discoveries could have. To explore those, he may choose to integrate these investigations with studies of more complex animals, he said.

"*C. elegans* provides a system where it may be possible to have a full quantitative understanding of how brain activity arises and generates behavior," he said. "A key challenge as we move forward is to take stock of what we're learning and apply these lessons in bigger brains."



Gloria CHOI

"[How can we] ... try to use the knowledge to be able to regulate how the brain works and improve symptoms of various neurological disorders?

Neuroscientists are beginning to appreciate that, for better and worse, the immune system communicates with the brain. Gloria Choi is studying their conversations to make new discoveries and even taking control of them to see if that can improve mental health.

"I'm trying to actually decipher the language that is spoken between these two systems," said Choi, Mark Hyman Jr. Career Development Associate Professor. "Can we understand it enough such that we not only know how the brain functions but also try to use the knowledge to be able to regulate how the brain works and improve symptoms of various neurological disorders?"

It may seem like an adventurous notion, especially given that many scientists once thought the brain was walled off from the vagaries of the body's immune system. But Choi's neuroscience research has provided powerful demonstrations of how consequential neuroimmune conversations can be. Via her close collaboration with her husband Jun Huh, a Harvard immunologist, Choi can eavesdrop on both ends of the proverbial phone line.

"We can utilize each of our expertise and thereby be able to ask questions in a way that perhaps no other people can, just because we are working together," said Choi, who joined The Picower Institute in 2019.

Over the last several years, for instance, their labs have found an answer for why maternal infection during pregnancy is associated with an elevated risk for the child to develop autism. In a series of papers in 2016 and 2017 using mouse models, they discovered that if a pregnant dam harbored certain microbiome bacteria and then became infected, that would prompt specific immune cells to produce too much of a molecule called Il-17a. Upon reaching receptors in brain cells of the fetus, IL-17a hindered neural development, leading to hyperexcitation in the S1DZ region of the cortex. The resulting altered circuit activity led to autism-like social behaviors in the offspring as adults.

Counterintuitively, Choi and Huh's team also showed in 2019 that when those adult offspring get sick, their own overproduction of IL-17a could reduce excitation in S1DZ. That explained another clinical mystery of why some people with autism seem to exhibit improved social behaviors when running a fever. It's not the fever, per se, but the neuroimmune conversation in the language of IL-17a.

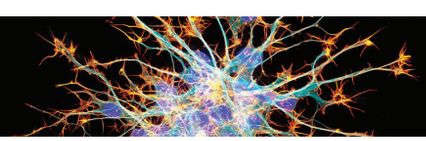
Taken together the studies provide many potential targets for intervention. For instance, Choi's experiments increasing or decreasing IL-17a levels at different times in pregnant dams or their progeny improved social behavior outcomes.

Even before Choi came to MIT in 2013 and started focusing on neuroimmunology, she was interested in circuits underlying behavior. She earned her PhD at Caltech by discovering a brain circuit that helped animals choose between conflicting instincts (e.g. mating or fleeing danger). Then during her postdoc at Columbia, she studied the circuit mechanisms by which olfactory sensory inputs become linked to behavioral outputs through learning.

In a 2021 study, she blended both of those influences with an immunity-related context to discover a brain circuit in mice that enforces social distancing. Her lab found that male mice who smell that a female is ill will refrain from mating, thanks to a series of connections they uncovered in a brain region called the amygdala.

Choi's studies have produced a number of intriguing new questions that she plans to pursue next. For instance, the social distancing study showed how a mammal's brain is wired to integrate sensory context with internal intentions to override an instinct that would make it sick. Choi wants to explore that potential platform's broader significance, for instance to see how immune and neural signaling molecules each modulate such circuits. She also plans to investigate how the S1DZ region of the cortex exerts such a profound effect on social behaviors.

And Choi also has begun to chart how other immune molecules beyond IL-17a influence the brain. With accumulating evidence, she hypothesizes that immune signaling may influence conditions as diverse as depression and Alzheimer's disease. By learning that signaling language, she may also reveal novel ways to intervene.



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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.

COVER: Neurons from stem cells, fluorescence light micrograph.
Dr. Torsten Wittman / Science Photo Library