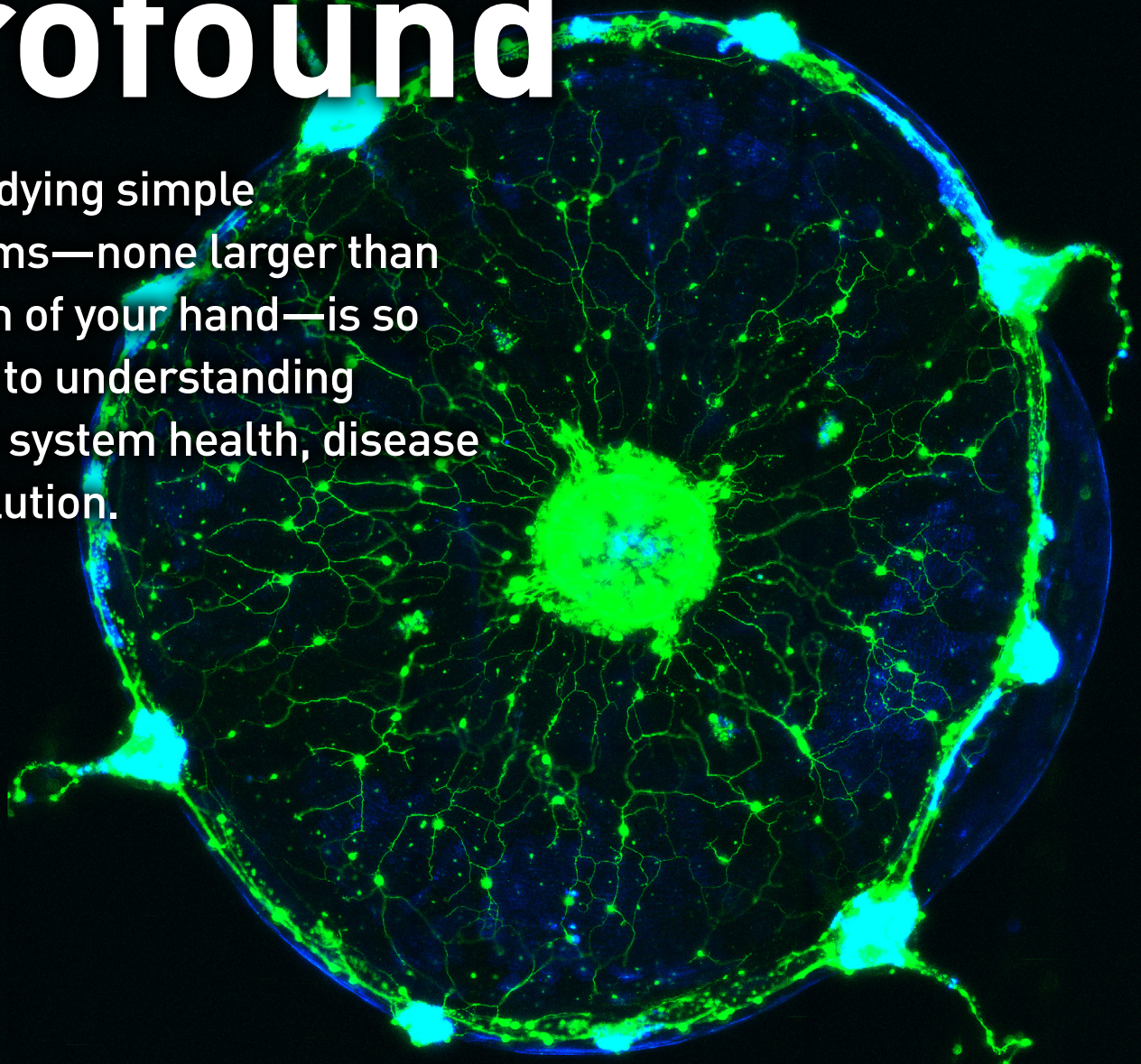
INSIDE

Petite & Profound

Why studying simple organisms—none larger than the palm of your hand—is so integral to understanding nervous system health, disease and evolution.

Pg. 10



Neuroscience News

MIT SUMMER 2023

THE PICOWER INSTITUTE FOR LEARNING AND MEMORY

DIRECTOR'S **MESSAGE**

Dear Friends,

In science the next best thing to making discoveries may be getting the chance to ask questions to begin with. Launching new research, not just succeeding in it, is a thrill. It can be exhilarating to conceive and contemplate new ideas.

In this edition of *Neuroscience News* we celebrate these moments of new questions and new discoveries in a few different ways. On page 8 we proudly announce that two new MIT faculty members have joined The Picower Institute. Assistant Professors Sara Prescott and Brady Weissbourd each recently have launched labs in the biology department and are embarking on exciting research that brings entirely new questions about entirely new systems into our community.

In our cover story (page 10) we pose an overarching question: Why do we seek to learn about the nervous system by studying tiny, simple organisms that, at first glance, seem to barely have any resemblance to us? As you'll see, the answer lies in both in the unique ways that they enable us to ask crucial questions, and also in the discoveries they've helped us to make.

This edition is also chock full of news about our discoveries. There are stories about new advances in research on Alzheimer's, and on the nature of memory, learning and consciousness. But a particularly momentous discovery we report on (this page) is one made in 2009. Back then Newton Professor Mriganka Sur showed that mice modeling the devastating neurodevelopmental disorder Rett syndrome lacked a protein called IGF-1, which he had discovered helps neural connections mature. His lab further showed that administering an IGF-1 peptide had strong therapeutic benefits. An unrelated company that had an IGF-1 drug took that cue all the way through clinical trials leading on March 10 to the first FDA-approved therapy for Rett. That success, which promises to improve many lives, traces back to the Sur lab's pivotal insight.

When answers can be that wonderful, it's no wonder that we revel in asking the questions that lead to them. We hope you'll revel in reading about that here.

LI-HUEI TSAI, DIRECTOR

The Picower Institute for Learning and Memory

3 questions for Mriganka Sur: **The research basis of the first approved drug to treat Rett syndrome**

Rett syndrome is a devastating developmental disorder, principally occurring in girls, caused by mutations in the gene MECP2 that leads to severe cognitive, motor and other symptoms. That's why the March 10 approval by the U.S. Food and Drug Administration of the first-ever treatment for the disorder, a drug called Trofinetide based on the natural protein IGF-1, has brought new hope to patients and their families.

The approval was also a dream come true for Mriganka Sur, Newton Professor of Neuroscience in The Picower Institute for Learning and Memory and the Department of Brain and Cognitive Sciences at MIT. His lab's preclinical discoveries in mice, particularly a seminal paper published in 2009, provided the first demonstration that injecting IGF-1 or its peptide fragment could reverse the effects of reduced or altered MECP2. This provided a mechanism-based rationale for IGF-1 as a potential therapeutic intervention, later tested clinically with Trofinetide by an unrelated company.

Sur's research began nearly 20 years ago when his lab was studying a famous phenomenon in neuroscience: When an animal's eye is blocked during a critical period of development, the brain shifts neural connections called synapses to devote more brainpower to the unblocked eye. Sur's lab investigated the molecules involved in this flexibility, or "ocular dominance plasticity," and discovered IGF-1's role. His lab has never stopped studying Rett syndrome since.

How did your lab discover that IGF-1 might be a potential Rett syndrome therapeutic?

We decided to study the molecular basis of ocular dominance plasticity using a large-scale, unbiased screen. An interesting gene set that changed when an eye was closed was the IGF-1 gene set named for the growth factor IGF-1. When we checked one week after closing the eye, a binding protein for IGF-1 had gone up. It soaked up a lot of IGF-1. That suggested that to make connections change you must decrease molecules like IGF-1.

This was published in a paper in 2006 in *Nature Neuroscience*, where Daniela Tropea, who was a postdoc in the lab, led the experiments. The icing on the cake was when Daniela delivered a peptide form of IGF-1 to the brain. When she did that and closed the eye, thereby overcoming the reduction of IGF-1, then this shift of synapses did not happen. The addition of IGF-1 into the brain stabilized synapses and made them resistant to change, essentially making them adult-like.

In 2007 the lab of Adrian Bird in Edinburgh made a mouse line in which they could keep MECP2 in check for the first 5 or 6 weeks of life, so that the mice began to develop Rett syndrome-like symptoms. But then Adrian's lab turned the gene back on and the mice largely recovered. I was immediately struck by this discovery. It showed that Rett Syndrome is not a disorder of degeneration, it is a disorder of aberrant and even abnormally prolonged development: loss of MECP2 likely reduces molecules that the brain requires for normal development, but adding back these molecules could enable the brain to develop normally, at least to some extent.

The developing brain shows pronounced plasticity, as demonstrated by ocular dominance plasticity in visual cortex. This plasticity occurs only during early life, and not later. If mice missing MECP2 had aberrantly prolonged development, they should show this plasticity later in life as well. Daniela and I decided to do an experiment to test this idea. We asked whether we could use our visual cortex paradigm to ask is there prolonged plasticity into adulthood in Rett model mice and can we reverse it by adding IGF-1? We did this using Rett model mice from the lab of Rudolf Jaenisch at the Whitehead Institute.

Unlike in normal mice where there is only a critical time window of plasticity in the visual cortex, Rett model mice showed an effect of closing one eye even in adulthood. We immediately then asked, is there reduced IGF-1 in the brain and there was, and there was increased IGF-1 binding protein. These mice were in a state of perpetual plasticity.

Mriganka Sur discussed his Rett syndrome research at the Picower Institute's 20th Anniversary Exhibition in 2022. Credit: Faith Ninivaggi

We reasoned if we could give adult Rett model mice a peptide form of IGF-1 via injection the effect of this perpetual plasticity should go away, meaning that the animals should not show an effect of the eye being closed – as occurs when mice normally mature. And that's what happened. We showed that IGF-1 peptide increased expression of a number of synaptic molecules and made excitatory synapses stronger. This provided a powerful mechanism for explaining the effects of the drug. Finally we asked, do the mice do better in other ways? We found that the mice lived longer, that they moved better and other symptoms improved.

We published that discovery in 2009 in *PNAS*: In a mouse model we showed that by understanding the molecules underlying Rett syndrome's prolonged development and plasticity we could intervene to potentially offset the molecular and synaptic deficits and treat the disorder. This is the foundational discovery behind Trofinetide and its mechanism of action in Rett syndrome.

Tell us about your lab's continued work on fundamental mechanisms Rett syndrome?

We've never stopped working on Rett syndrome. It's a devastating disorder and there is certainly still much left to learn.

In 2014 we published another paper in *PNAS* showing that doses of recombinant human IGF1 were effective in mice. And I was also the co-author in that same journal later that year showing encouraging results in a small human clinical trial.

We've also done more research, right up to the present day, to understand the fundamental mechanisms of how the genetic mutations perturb brain development. In 2017 using induced stem cell cultures derived from patients and normal subjects, we found that when MECP2 is lacking, microRNAs critical to proper brain development become misregulated. Overexpression of the microRNAs prevented new neurons from being born, whereas inhibiting the microRNAs enabled healthy neural birth. This was a surprisingly early effect of Rett Syndrome that we demonstrated directly in human neurons and their progenitors.

Last year we used an innovative combination of advanced imaging methods and human stem cell-derived organoids to show that in Rett syndrome, the migration of neurons to the cerebral cortex becomes much slower and highly erratic. These discoveries lead to the sobering realization that there can be very early changes in brain development due to the genetic mutations of Rett syndrome.

What is the significance of seeing this basic research achieve clinical utility and impact?

By studying plasticity in normal mice and the fundamental mechanisms by which synapses change, and hence change brain function and behavior, we moved into analyzing the effect of a gene that underlies a devastating brain disorder. IGF-1 peptide has become the very first molecule to reach this stage for any developmental brain disorder in that it is a mechanism based therapeutic. Based on an animal model and doing the mechanistic analysis of why does the gene affect the brain and how might we offset it, we set the course for the first drug to treat Rett syndrome.

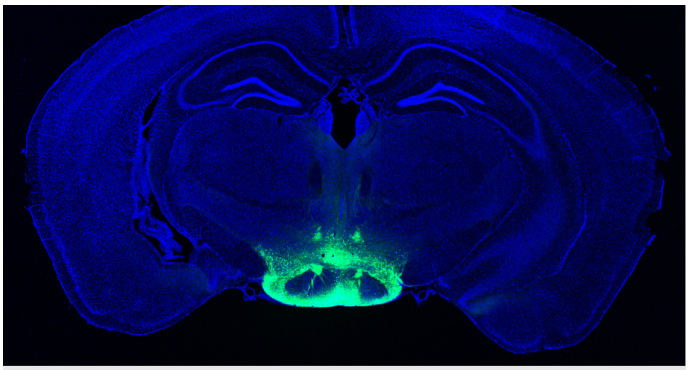
A lot of the early work was Daniela's insight in terms of how to think about basic mechanisms of developmental plasticity and apply them to brain disorders. This was completely uncharted territory as to whether plasticity would be a phenomenon underlying developmental disorders, and whether the visual cortex in the mouse could then model the disorder. And finally we had the idea that a molecule that has a role in regulating this plasticity can be applied to the disorder. Many ideas in science don't work out but this one did. Several people from my lab participated in the discovery. We also could not have tested these ideas without our collaboration with Rudolf Jaenisch and his lab. He was very generous with his lab's resources – we had no grant funds for this work at that time – and our labs have now collaborated on several studies since then.

It is the dream of every neuroscientist to have an impact on the world in some way. And this is my dream come true!

Study pinpoints neurons especially vulnerable to **Alzheimer's**

One of the first brain regions to show neurodegeneration in Alzheimer's disease is a part of the hypothalamus called the mammillary body. In a new study, MIT researchers have identified a subset of neurons within this body that are most susceptible to neurodegeneration and hyperactivity. They also found that this damage leads to memory impairments.

The findings suggest that this region may contribute to some of the earliest symptoms of Alzheimer's disease, making it a good target for potential new drugs to treat the disease, the researchers say.



Staining highlights neurons in the mammillary body of an Alzheimer's model mouse's brain.

"It is fascinating that only the lateral mammillary body neurons, not those in the medial mammillary body, become hyperactive and undergo neurodegeneration in Alzheimer's disease," said senior author Li-Huei Tsai, director of MIT's Picower Institute and Aging Brain Initiative.

The researchers showed in mice that they could reverse memory impairments caused by hyperactivity and neurodegeneration in mammillary body neurons by treating them with a drug that is now used to treat epilepsy.

Former MIT postdoc Wen-Chin (Brian) Huang and MIT graduate students Zhuyu (Verna) Peng and Mitchell Murdock are the lead authors of the paper in *Science Translational Medicine*.

As Alzheimer's disease progresses, neurodegeneration occurs along with the buildup of amyloid beta plaques and misfolded Tau proteins, which form tangles in the brain. One question that remains unresolved is whether this neurodegeneration strikes indiscriminately, or if certain types of neurons are more susceptible.

"If we could identify specific molecular properties of classes of neurons that are predisposed to dysfunction and degeneration, then we would have a better understanding of neurodegeneration," Murdock says. "This is clinically important because we could find ways to therapeutically target these vulnerable populations and potentially delay the onset of cognitive decline."

In a 2019 study using a mouse model of Alzheimer's disease, Tsai, Huang, and others found that the mammillary bodies — a pair of structures found on the left and right underside of the hypothalamus — had the highest density of amyloid beta.

To learn more about the mammillary body's function, the researchers used single-cell RNA-sequencing, which can reveal the genes that are active within different types of cells in a tissue sample. They identified two major populations of neurons: one in the medial mammillary body and the other in the lateral mammillary body. In the lateral neurons, genes related to synaptic activity were very highly expressed.

The researchers wondered if the lateral neurons might be more susceptible to Alzheimer's. The researchers found that Alzheimer's model mice showed much more hyperactivity in lateral mammillary body neurons than healthy mice. However, the medial mammillary body neurons in healthy mice and the Alzheimer's model did not show any such differences.

The researchers found that this hyperactivity emerged very early — around two months of age (the equivalent of a young human adult), before amyloid plaques begin to develop. The lateral neurons became even more hyperactive as the mice aged, and these neurons were also more susceptible to neurodegeneration than the medial neurons.

The Alzheimer's mouse model showed impairments in forming new memories, but when the researchers treated the mice with a drug that reduces neuronal hyperactivity, their performance on memory tasks was significantly improved. This drug, known as levetiracetam, is used to treat epileptic seizures and is also in clinical trials to treat hyperexcitability in the cortex, which increases the risk of seizures — in Alzheimer's patients.

The researchers also studied human brain tissue from the Religious Orders Study/Memory and Aging Project. Using single-cell RNA-sequencing of mammillary body tissue from people with and without Alzheimer's, the researchers found two clusters of neurons that correspond to the lateral and medial mammillary body neurons they found in mice.

The researchers also found signatures of hyperactivity in the lateral mammillary bodies of the human tissue samples, including overexpression of genes that encode potassium and sodium channels. They also found higher levels of neurodegeneration in the lateral neuron cluster, compared to the medial cluster.

Other studies of Alzheimer's patients have found a loss of volume of the mammillary body early in the disease, along with deposition of plaques and altered synaptic structure. All of these findings suggest that the mammillary body could make a good target for potential drugs, the researchers say.

Tsai's lab is now working on further defining how the lateral neurons of the mammillary body are connected to other parts of the brain to figure out how they form memory circuits. The researchers also hope to learn more about what properties of the lateral neurons of the mammillary body make them more vulnerable to neurodegeneration and amyloid deposition.

Peptide might help treat Alzheimer's

MIT neuroscientists have found a way to reverse neurodegeneration and other symptoms of Alzheimer's disease by interfering with an enzyme that is typically overactive in the brains of Alzheimer's patients.

When the researchers treated mice with a peptide that blocks the hyperactive version of an enzyme called CDK5, they found dramatic reductions in neurodegeneration and DNA damage in the brain. These mice also showed improvements in their ability to perform tasks such as learning to navigate a water maze.

"We found that the effect of this peptide is just remarkable," said Picower Professor Li-Huei Tsai, director of The Picower Institute and the senior author of the study. "We saw wonderful effects in terms of reducing neurodegeneration and neuroinflammatory responses, and even rescuing behavior deficits."

With further testing, the researchers hope that the peptide could eventually be used as a treatment for patients with Alzheimer's disease and other forms of dementia that have CDK5 overactivation. The peptide does not interfere with CDK1, an essential enzyme that is structurally similar to CDK5, and it is similar in size to other peptide drugs that are used in clinical applications.

Picower Institute Research Scientist Ping-Chieh Pao is the lead author of the paper in the *Proceedings of the National Academy of Sciences*.

As a postdoc, Tsai identified and cloned the CDK5 gene, which plays important roles in the development of the central nervous system, and also helps to regulate synaptic function.

CDK5 is activated by a smaller protein known as P35. When P35 binds to CDK5, the enzyme's structure changes, allowing it to add a phosphate molecule to its targets. However, in Alzheimer's and other neurodegenerative diseases, P35 is cleaved into a smaller protein called P25, which can also bind to CDK5 but has a longer half-life than P35.

When bound to P25, CDK5 becomes more active in cells. P25 also allows CDK5 to phosphorylate molecules other than its usual targets, including the Tau protein. Hyperphosphorylated Tau proteins form the neurofibrillary tangles that are one of the characteristic features of Alzheimer's disease.

Tsai's lab has shown that transgenic mice engineered to express P25 develop severe neurodegeneration. In humans, P25 has been linked to several diseases, including not only Alzheimer's but also Parkinson's disease and frontotemporal dementia.

Pharmaceutical companies have tried to target P25 with small-molecule drugs, but these drugs tend to cause side effects because they also interfere with other cyclin-dependent kinases.

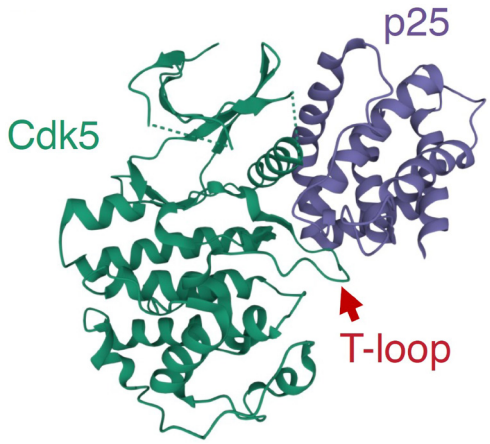
The MIT team decided to take a different approach to targeting P25, by using a peptide instead of a small molecule. They designed their peptide with a sequence identical to that of a segment of CDK5 known as the T loop, which is a structure critical to the binding of CDK5 to P25. The entire peptide is only 12 amino acids long — slightly longer than most existing peptide drugs, which are five to 10 amino acids long.

In tests in human neurons grown in a lab dish, the researchers found that treatment with the peptide led to a moderate reduction in CDK5 activity. Those tests also showed that the peptide does not inhibit the normal CDK5-P35 complex, nor does it affect other CDKs.

When the researchers tested the peptide in a mouse model of Alzheimer's that has hyperactive CDK5, they saw beneficial effects including reductions in DNA damage, neural inflammation, and neuron loss.

Peptide treatment also produced dramatic improvements in a different mouse model of Alzheimer's, which has a mutant form of the Tau protein that leads to neurofibrillary tangles. After treatment, those mice showed reductions in both Tau pathologies and neuron loss.

Mice treated with the peptide performed much better in a task that required learning to navigate a water maze, which relies on spatial memory, than mice that were treated with an inert control peptide.



A new peptide disrupts binding of the enzyme Cdk5 with the protein p25 by targeting the enzyme's T loop.

The researchers also analyzed the changes in gene expression that occur in mouse neurons following treatment with the peptide. Among the changes they observed was an increase in expression of about 20 genes that are typically activated by a family of gene regulators called MEF2. Tsai's lab has previously shown that MEF2 activation of these genes can confer resilience to cognitive impairment in the brains of people with Tau tangles.

Tsai now plans to do further studies in other mouse models of diseases that involve P25-associated neurodegeneration, such as frontotemporal dementia, HIV-induced dementia, and diabetes-linked cognitive impairment.

"It's very hard to say precisely which disease will most benefit, so I think a lot more work is needed," she said.

In a simple animal, study reveals **serotonin's** effects

Serotonin is the most common target of psychiatric drugs but scientists need to learn much more about how the molecule affects brain cells and circuits. In *Cell*, researchers at The Picower Institute working in a simple animal model achieved a comprehensive accounting of how serotonin affects behavior from the scale of individual molecules all the way to the animal's whole brain.

"There have been major challenges in rationally developing psychiatric drugs that target the serotonergic system," said Lister Brothers Associate Professor Steve Flavell. "The system is wildly complex."

The same sources of complexity exist in the nematode worm *C. elegans*, but to a more manageably limited degree than in humans. *C. elegans* has only 302 neurons (rather than billions) and only six serotonin receptors (rather than 14). All *C. elegans* neurons and their connections have been mapped out and its cells are accessible for genetic manipulation. Moreover, Flavell's team has developed imaging technologies to track and map neural activity across the worm's brain.

The researchers identified the functional roles of the worm's six serotonin receptors by creating 64 different mutant strains covering the different combinations of knocking out the various receptors. In each strain they stimulated the neuron NSM, which releases serotonin to slow locomotion. Analysis revealed that three receptors primarily drove the slowing behavior. The other three receptors "interacted" with those, modulating how they function. Another insight was that different receptors respond to different patterns of serotonin release. Complex interactions among serotonin receptors in the control of behavior is likely to be directly relevant to psychiatric drugs that target these receptors, Flavell said.

Looking across the whole brain, Flavell's lab mapped each neuron's serotonin receptor expression. Then the team observed how NSM affected each neuron's activity as worms freely explored. About half of the neurons across the worm's brain changed activity when serotonin was released. Ultimately, by knowing each neuron's circuit connections and which receptors each neuron expressed, the team was able to make strong predictions about how each neuron's activty was impacted by serotonin.

Serotonin molecule.

'Spatial Computing' enables flexible working memory

Routine tasks that require working memory, like opening a padlock, involve remembering general task rules (e.g. turn left, then right, then left again) and some specific content for each instance (e.g. 23, 16, 29). A new study in *Nature Communications* provides a novel explanation for how the brain distinctly manages the general and specific components of such cognitive demands.

The brain creates distinct spaces in the cortex for each general rule and controls those patches with brain rhythms, a concept the authors call "Spatial Computing." This system, evident in the study's experiments in animals, explains how the brain can easily sustain a consistent understanding of a process even when the specific contents keep changing. It also answers a few questions neuroscientists have wrestled with about the physiological operations that underlie working memory.

"Your brain can instantly generalize. If I teach you to follow some rules, like remembering C, A, and B and putting them into alphabetical order, and then I switch the contents to F, D and E you wouldn't miss a beat," said Earl K. Miller, Picower Professor in The Picower Institute. "Your brain can do this because it represents the rules and the contents at different physical scales. One can just be plugged into the other."

Years of research by Miller's lab, much of it led by lead author Mikael Lundqvist now at the Karolinska Institute have shown that working memory tasks are governed by an interplay of brain waves at distinct frequencies. But these waves operate on networks of millions of neurons, only a smattering of which store the individual items of information relevant at any particular time. Moreover, neurons that carry information about specific items are found all over the place.

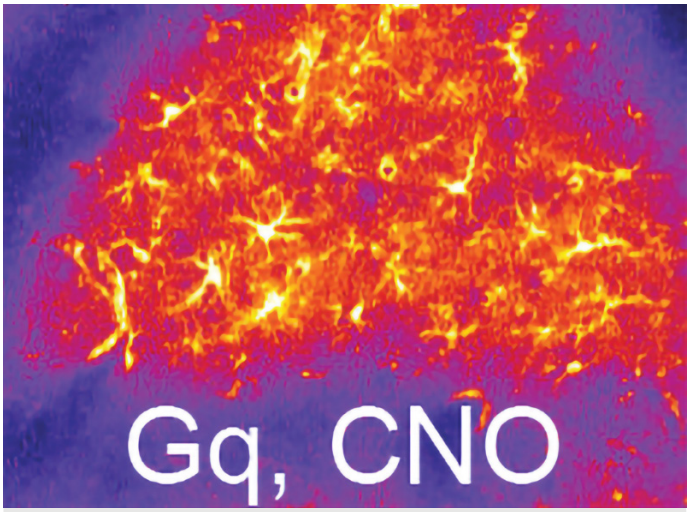
In the Spatial Computing theory, individual neurons representing information items can be scattered widely, but the rule that's applied to them is based on the patch of the network they are in. Those patches are determined by the pattern of beta and gamma waves.

The researchers tested Spatial Computing in real physical brains. They made four experimental predictions about what they should observe as animals played working memory games. In all cases the results matched the predictions.

Astrocyte cells critical for **learning** skilled movements

You might think that learning a new golf swing or dance move is only implemented by neurons, but a new study by Picower Institute researchers shows the essential role of another brain cell type: astrocytes.

Just as teams of elite athletes train alongside staffs of coaches, ensembles of neurons in the brain's motor cortex depend on nearby astrocytes to help them learn to encode when and how to move, and the optimal timing and trajectory of a motion, the study shows. Experiments in mice described in the *Journal of Neuroscience* reveal two specific ways that astrocytes directly impact motor learning, maintaining an optimal molecular balance in which the neuronal ensembles can properly refine movement performance.



Researchers disrupted motor learning in mice when they increased Gq signaling and calcium activity in astrocytes with a chemical called CNO.

"This finding is part of a body of work from our lab and other labs that elevate the importance of astrocytes to neuronal encoding and hence to behavior," said senior author Mriganka Sur, Newton Professor in The Picower Institute.

Sur's team gave mice a simple motor task to master. When cued with a tone, the mice had to reach for and push down a lever within five seconds.

In some of the mice, however, the team employed precision molecular interventions to disrupt two specific functions of astrocytes in the motor cortex. The interventions each affected the performance of the mice in distinct ways. In some mice, they disrupted the astrocytes' ability to soak up the neurotransmitter glutamate, a chemical that excites neural activity when it is received at connections called synapses. In other mice they hyperactivated the astrocytes' calcium signals, which affected how they function. In both ways, the interventions disrupted the normal process by which neurons would form or change their connections with each other, a process called "plasticity" that enables learning.

Each intervention distinctly disrupted how well the mice learned. In the study the team identified underlying changes in neural activity and in astrocyte gene expression resulting from the interventions.

Studying **consciousness** without affecting it

In science it's often hard to measure a system without the measurement affecting the system. Researchers assessing consciousness, for instance as volunteers receive anesthesia, typically use sound to see if subjects can still respond, but that sound might keep them awake longer or wake them up sooner than normal. A new study in the *British Journal of Anesthesia* validates a way to assess consciousness without external stimulation and finds that it may be more precise.

Before infusing patients with dexmedetomidine anesthesia, the team led by Picower Institute research affiliate Christian Guay instructed 14 volunteers to squeeze a force sensor with their hand whenever they breathed in and release it when they breathed out. Then the drug started flowing. When subjects stopped performing the "breathe-squeeze test," they were judged to have lost responsiveness and when they resumed after dosing tapered off, they were judged to have regained responsiveness. Importantly, after the initial instruction there was no ongoing external stimulation from the researchers. The task was internally prompted.

All along, the researchers recorded the subjects' brain rhythms using 64 electrodes around the scalp. They observed telltale patterns of dexmedetomidine effects—for instance a decline in ~10Hz "alpha" rhythm power in the occipital region followed by an increase in power of much slower "delta" waves as people lost responsiveness and then a reversal of that when they woke up. Because of their approach they didn't see artifacts of auditory stimulation that disrupted those patterns in a previous study. Moreover, estimates of drug concentration in the brain during the two studies suggest that the breathe-squeeze method detected loss of responsiveness at lower concentrations of the drug than the sound-stimulation method, suggesting it is more sensitive.

"This approach for assessing loss and recovery of consciousness removes the significant confound of the conventional external stimulus that is typically used," said study co-senior author Emery N. Brown, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience in The Picower Institute. "We are eager to apply the technique in our studies of other anesthetics."

New investigators broaden institute's research

Sara Prescott studies 'interoception' —the brain's sense of the body's organs—while Brady Weissbourd examines behavior and evolution in a new model: jellyfish.

This spring two new MIT faculty members joined The Picower Institute, bringing unique research programs that expand the scope of the Institute's neuroscience studies.

In distinct ways, Sara Prescott and Brady Weissbourd, who are both assistant professors in the Department of Biology, are looking beyond the brain to understand more about how behaviors emerge from nervous system structure and activity at scales from genes and molecules to whole circuits and networks.

Biology Assistant Professor and Picower Institute Investigator Sara Prescott

Prescott focuses on the important influence of the "interoceptive" signals the body's internal organs send to the brain, particularly along the far-reaching vagus nerve. As a postdoc at Harvard in the lab of Stephen Liberles, she looked at the airway in mouse models, identifying a wide diversity of neurons there including a rare type specifically responsible for triggering protective responses like coughing when water or acid enters the airway. She also helped discover a separate population of neurons that make us feel and act sick when we get a flu infection.

At MIT Prescott continues to study the mouse airway, asking questions such as how long-term insults including respiratory infections may cause fundamental remodeling of neural circuits and epithelial tissues, for instance to adapt to future threats. Her lab is also developing lab models of airway surfaces to gain insight into how the airway senses irritants.

Read an interview with Prescott

Read an interview with Weissbourd

Biology Assistant Professor and Picower Institute Investigator Brady Weissbourd

Weissbourd's interest in understanding how organisms generate behaviors based not only on their senses but also their internal needs and drives led him to develop an entirely new model: the tiny, transparent jellyfish *Clytia hemisphaerica*. During postdoctoral work at Caltech in the lab of David Anderson, Weissbourd established methods for genetically manipulating the jellyfish, which have highly structured but flexible networks of a few thousand neurons (but no central brain), so that they can be models for neuroscience study at a complex but tractable scale.

In one arm of his MIT lab, Weissbourd will study how jellyfish behaviors emerge from their nervous system organization and activity, potentially helping to identify and illuminate fundamental principles and mechanisms common to all animals. But in another arm, he'll look at how the unique evolution of the jellyfish, which diverged from ours about 600 million years ago, can shed light on the earliest nervous systems and provide lessons from the remarkable diversity of nervous systems in nature. Jellyfish, for instance, have the enviable ability to rapidly add new neurons and to therefore restore function even after severe injury.

Despite studying distinct questions and systems, both Prescott and Weissbourd have already embarked on early collaborations with fellow Picower Institute investigators. Prescott is working with Picower Professor and Institute Director Li-Huei Tsai to explore whether and how non-invasive sensory stimulation can alleviate inflammation at visceral organs like the airways and gut. Weissbourd has teamed up with Sherman Fairchild Professor Matt Wilson to examine whether jellyfish exhibit sleep and how that affects their nervous systems.

"We are very excited to welcome Brady and Sara into our community," Tsai said. "They are both outstanding young scholars whose research will give us a much fuller and richer understanding of questions including how nervous systems help organisms survive and thrive by producing behaviors based on their circumstances."

High schoolers see science up close during spring break

Even during MIT's spring break the halls of the university's life sciences buildings were still teeming with young students. That's because on March 29 and 30 scores of students from six area high schools filled the void by the busload to learn about biology and brain science, including from several members of The Picower Institute.

On March 29, for instance, groups of Wellesley students visited with postdoc Matheus Victor and technical associate Áine Ni Scannail to learn how the lab of Picower Professor Li-Huei Tsai cultures human brain cells to study Alzheimer's disease. The cultures, derived directly from patients' skin cells, can be used to test how different genes contribute to Alzheimer's disease pathology and can provide a testbed for whether different drugs could help reduce it.

More than 80 students from Everett and Lawrence gathered March 30 to learn about the neuroscience of jellyfish from biology Assistant Professor Brady Weissbourd. With vibrant videos and images, Weissbourd explained that the jellyfish nervous system has both amazing differences from humans, like an uncanny ability to regenerate, and important similarities, including the same basic job of generating appropriate behaviors based on their current state and environment.

Graduate student Andrés Crane led groups of Lawrence High School students through the lab of Menicon Professor Troy Littleton, who uses fruit flies to study fundamentals of how neurons communicate, for instance to control muscle. Crane explained how the researchers can make mutations in the flies to study how those affect the molecules that neurons use to create and operate their connections, or "synapses," with muscles or other neurons.

From their visit with Crane the students then went to the lab of Picower Professor Mark Bear, where postdoc David Stoppel showed how he uses mice to study fragile X syndrome, a form of autism. Stoppel demonstrated how he prepares mouse brains so that he can make comparisons about how brain activity differs in neurotypical mice and ones modeling the genetics of fragile X. He showed the high schoolers how brain tissue from the visual cortex of mice modeling the disease shows much greater activity upon electrical stimulation than the tissue from typical mice.

Littleton Lab graduate student Andrés Crane introduces students from Lawrence High School to electrophysiology techniques.

This spring The Picower Institute welcomed its newest affiliate faculty member, **Laura Lewis,** Athinoula A. Martinos Associate Professor in the Department of Electrical Engineering and Computer Science and MIT's Institute for Medical Engineering and Science. Lewis who earned her PhD in 2014 in the Picower Institute lab of Emery N. Brown, became an MIT faculty member in February after serving as an assistant professor at Boston University. Her research focuses on neuroimaging approaches that better map brain function, with a particular focus on sleep. She is developing computational and signal processing approaches for neuroimaging data and applying these tools to study how neural computation is dynamically modulated across sleep, wake, attentional, and affective states.

Congratulations to new **Picower PhDs**

Six graduate students in Picower Institute labs earned PhD's recently. Their research spanned diverse topics: The cells that compose the brain's blood vessels and how they matter to health and disease; analyses of how a worm's nervous system produces its behaviors; ways to map the human brain in fine detail; study of a protein critical for the structural integrity of the axon projections neurons use to send signals across synaptic connections; and research on another protein important for ensuring proper neurotransmitter release at those synaptic junctions.

Flavell lab graduate student Jungsoo Kim defends his doctoral thesis

CONGRATULATIONS TO THEM ALL:

Dr. Adam Atanas, *Flavell Lab:* "Brain-wide representations of behavior spanning multiple timescales and states in *C. elegans*"

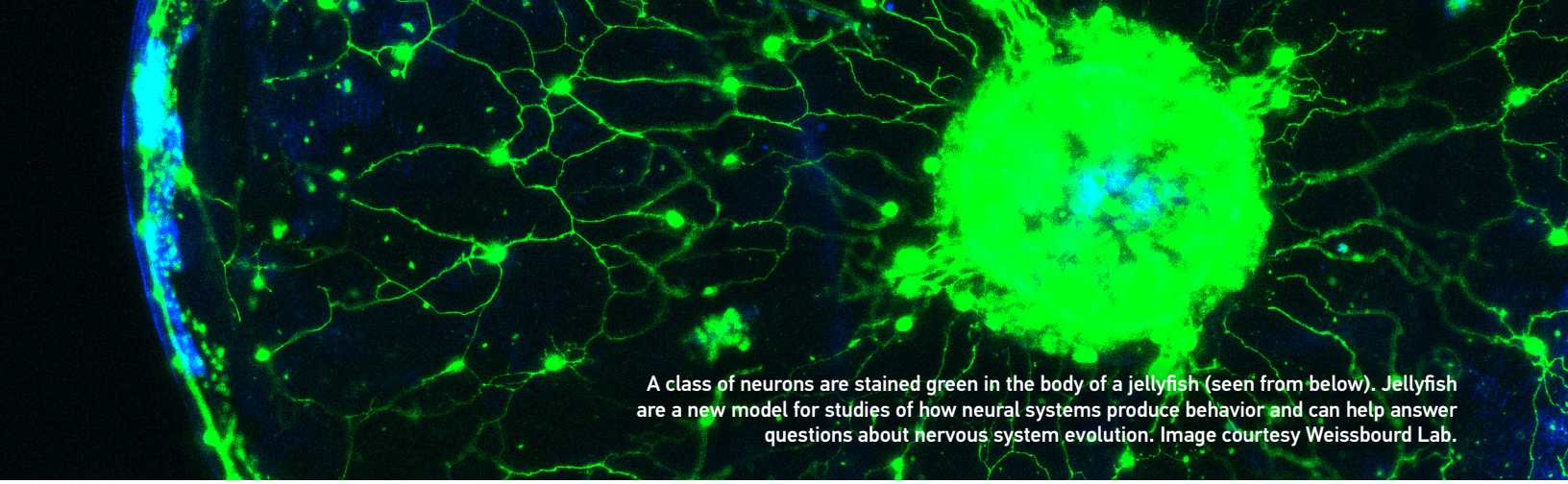
Dr. Elizabeth Brija, *Littleton Lab,* "Stochastic RNA editing of the Complexin C-terminus within single neurons regulates neurotransmitter release in Drosophila"

Dr. Francisco Garcia, *Heiman Lab,* "Molecular Profiling and Mechanisms of Cerebrovascular Function in Health and Neurodegeneration"

Dr. Webster Guan, *Chung Lab,* "Scalable Subcellular Resolution Mapping of the Human Brain"

Dr. Ellen Guss, *Littleton Lab,* "The heparan sulfate proteoglycan Perlecan regulates axonal and synaptic stability"

Dr. Jungsoo Kim, *Flavell Lab,* "The Flexible Mind of a Worm: the atlas of brain-wide representations of behavior in *C. elegans*"



A class of neurons are stained green in the body of a jellyfish (seen from below). Jellyfish are a new model for studies of how neural systems produce behavior and can help answer questions about nervous system evolution. Image courtesy Weissbourd Lab.

Petite & Profound

Why studying simple organisms—none larger than the palm of your hand—is so integral to understanding nervous system health, disease and evolution.

You don't look through compound eyes as you fly. Your navigation isn't aided by four legs, a set of whiskers and a nose millimeters above the ground. You've never squirmed through a patch of bacteria to lay your eggs. And you can't use your umbrella-shaped body to swim, stinging your dinner as you go.

But what you do have are neurons that connect and communicate to endow your nervous system with all its abilities, and so do classic neuroscience model organisms like mice, *Drosophila melanogaster* fruit flies, and *Caenorhabditis elegans* worms, and a newcomer, the *Clytia hemisphaerica* jellyfish. Such species might seem to be curious candidates in which to ask meaningful questions about being human, but because they pack many of the same fundamental features into much simpler and experimentally tractable forms, they are valuable exemplars of nervous system function both in health and disease.

"The history of neuroscience shows that when we study the right animal to ask the right question—even animals that are very different from humans—we can reveal fundamental principles of how nervous systems work that are universal," said Lister Brothers Associate Professor Steven Flavell, whose research employs *C. elegans* to study how behaviors emerge from neural activity.

Picower Professor Susumu Tonegawa's 1987 Nobel Prize-winning immunology research involved mice. Picower Professors Li-Huei Tsai and Mark Bear have developed candidate therapies for Alzheimer's disease and autism in mice. And before the FDA on March 10 approved the first-ever treatment for the devastating neurodevelopmental disorder Rett syndrome, Newton Professor Mriganka Sur had to discover the central role of the protein IGF-1 in mice (see page 2). Crucially, the protein works the same way in people.

And while fundamental similarities have made many models influential to the point of being indispensable, understanding the many ways organisms differ is valuable, too. Looking across a diversity of nervous systems is the best way biologists can ascertain how they evolved. Learning the specific ways animal models of disease differ from humans can lead to ideas for improving those models and guide experimental interpretations. And studying what's unique in biology has inspired new technologies. Among many examples, scientists use green fluorescent protein, first discovered in jellyfish, to visualize the expression and location of key proteins in cells – a revolutionary research tool.

"We can learn incredible amounts just from understanding the weird biology that's out there," said Assistant Professor Brady Weissbourd. 'Breakthrough technologies come from studying amazing capabilities of organisms."

Health and disease mechanisms

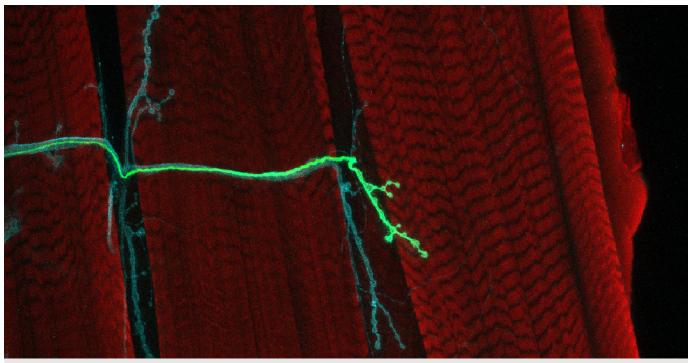
When a trait is found in multiple species, scientists say it is "conserved," because after it evolved in some ancestor organism, it stuck around in descendants, likely because it conveyed an important advantage.

Hundreds of millions of years ago nature evolved a method for neurons to connect and communicate in circuits and networks: releasing chemicals called neurotransmitters across synapses. In the research Menicon Professor Troy Littleton performs in flies to understand how synapses develop and function, almost all the genes and proteins he encounters have direct analogs (or "homologs") in humans. And because proper synapse function is so essential to brain health, Littleton's research into the molecular workings of fly synapses has led him to produce many insights about human diseases.

Fruit flies became popular models in neuroscience because they can be bred quickly and raised by the thousands in a lab. They can therefore be induced to rapidly produce genetic mutations that can be very informative about how genes function. If scientists want to know what a gene and the protein it encodes is good for, they can screen their flies until they find ones where it has mutated and see how that aberration affects the fly's function (nowadays scientists can also directly edit genes, of course).

Using genetic techniques, Littleton and his lab have characterized numerous proteins in synaptic development and function. When a neuron becomes electrically excited enough to send a signal, calcium

ions surge into synapses to trigger neurotransmitter release. Among other discoveries, Littleton's lab has shown that the number of calcium channels at release sites determines their strength and how much neurotransmitter they release, that the synaptic protein Complexin acts to prevent premature release of neurotransmitters until electrical signals are propagated into nerve terminals, and that the calcium-sensor Synaptotagmin 1 activates the process. He's also discovered that two other key synaptic proteins, Synaptotagmin 7 and Tomosyn, regulate how much neurotransmitter is available for release by controlling the number of synaptic vesicles, which store these small signaling molecules, that are staged at synapses.



The connections that fly neurons (magenta, green) make with muscle (red) are highly informative models of neural circuit connections called "synapses," which the Littleton lab studies to understand the basis of neuronal communication. Image courtesy Littleton Lab

Littleton's studies have also produced mechanistic insights into Huntington's disease, epilepsy, autism and neuropathy. For instance, in 2005 a genetic screen yielded a mutation that caused seizures, modeling epilepsy. Follow-up research showed that the mutation caused non-neural "glial" cells to retain too much calcium. In 2019 the lab discovered that the excess calcium overactivated a protein called calcineurin, disrupting the glial cells' removal of potassium ions from around neurons. That, in turn, meant neurons couldn't get rid of excess potassium, leaving them electrically overexcited and prone to seizures. The research therefore provided a way to potentially target seizures without having to alter neurons directly.

"Diseases and proteins that affect neurons can cause devastating outcomes, but to study how that happens you can't go into a human and manipulate them," Littleton said. "Being able to manipulate the homologs of those in Drosophila and to use genetic approaches to put them into gene pathway networks then allows you to go back into mammals and begin to look at whether there are conserved molecular networks around the disease protein."

Most Picower Institute labs work with mouse models because they, too, are small, easy to house and breed, and relatively simple compared to humans. But as mammals mice have brain cell types that match people closely—though not perfectly—and their brains are organized into regions (e.g. hippocampus) with functions (e.g. episodic memory) mimicking ours. Associate Professor Myriam Heiman's studies of Parkinson's disease, for instance, requires studying specific cell types in specific regions that mice and humans share.

"If we're interested in understanding the death of dopamine neurons in the midbrain, that's a relatively well conserved region between rodent and human brains," Heiman said.

In her lab's studies of neurodegenerative and psychiatric diseases, mice carrying human disease mutations can model how cells act and interact, circuits function and behaviors arise in health, disease and after potential treatments. She pairs such experiments and observations with analyses of postmortem human tissue.

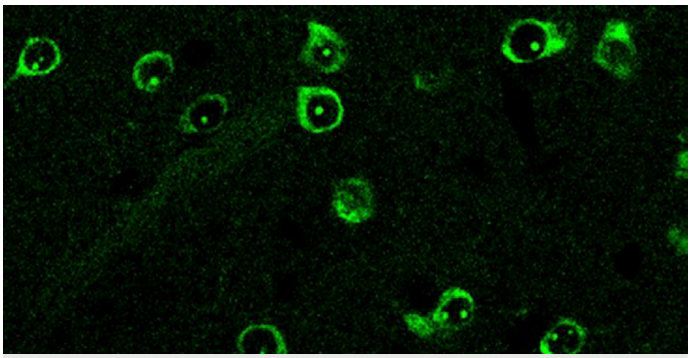
Heiman's use of mouse models has substantially advanced the field's understanding of Huntington's disease (HD), a devastating and so far untreatable neurodegenerative disease, by revealing new molecular mechanisms to target for therapies. In 2020 by performing an innovative genome-wide screen to delineate which genes promoted neural survival in HD model mice, Heiman identified the gene Nme1 and showed that increasing its expression in mice helped treat HD symptoms.

In another study that year, Heiman's lab showed in both human brain tissue and mouse models that a potentially major and early mechanism of disease in HD is RNA leaking out of damaged mitochondria. She found it triggers an errant and harmful innate immune response in neurons especially vulnerable to the disease. In a 2022 study that mapped all the key cell types in the brain's circulatory system both in healthy and HD humans and mice, the team saw the same sign of a misregulated immune response in the endothelial cells that help form the blood-brain barrier. The barrier protects the brain, so any harm to it could make disease worse.

Mice remain indispensable to Heiman's efforts to identify new therapeutic strategies. But in studies where she gathers analogous data from both humans and mice, she compares them not only to see what's the same, but also what's different to ensure that both the potential and limits of mouse models are better understood. In the brain vasculature study, for instance, her team showed that while both mice and people exhibit "zonation," or a difference in the cellular and molecular properties of arteries, veins and capillaries, the genes responsible in each species varied widely.

"Knowledge of these differences in zonation yields insight into differences in functionality between species," Heiman said, including why some methods for delivering treatments through the bloodstream may work in mice but not humans.

In the lab's newest paper, an analysis of what makes certain cell types especially vulnerable in ALS and Frontotemporal dementia, Heiman notes that key cells she and colleagues have pinpointed in humans aren't present in mice.

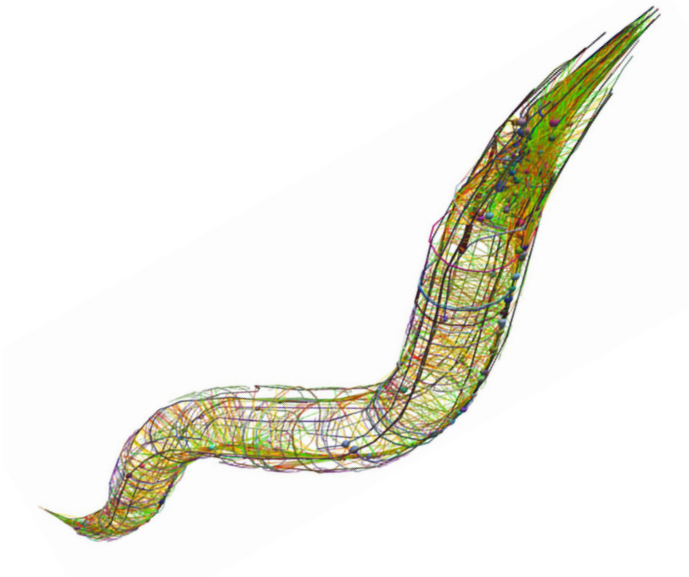


Spiny projection neurons in the brain's striatum are especially vulnerable to Huntington's disease. Mice have these cells and therefore provide a good model for studies aimed at understanding this vulnerability. Image courtesy Heiman Lab

New technologies including RNA sequencing cell by cell and the ability to engineer complex brain cell lab cultures from a human patient's skin cells have improved what neuroscientists can learn from human samples (see our Winter 2019 edition), but these technologies can't completely replace model organisms.

Complete behaving systems, simplified

Only a live organism can demonstrate how cellular and molecular activity produce learning and memory, perception, consciousness, or behavior, or model how those are altered by disease. For neuroscientists who want to understand how these phenomena emerge from a whole nervous system, that question is incredibly complex to ask even in a mouse or fly. To make headway Associate Professor Steven Flavell studies how sustained but flexible behaviors emerge in the *C. elegans* roundworm, which has just 302 neurons. Tiny and transparent, *C. elegans* can be readily raised, imaged and genetically manipulated. All the connections among its neurons have been mapped out.



A 3D rendering of a *C. elegans* worm, mapping all of its neurons. *C. elegans* allows scientists to study how neuromodulatory chemicals such as dopamine or serotonin affect behavior, cell by cell and brain-wide. Image courtesy Flavell Lab

These advantages make *C. elegans* a tractable model of the brain-behavior connection, but in no way an easy or trivial one. Flavell has had to invent new technologies (e.g an imaging system capable of tracking every behavior while simultaneously mapping the activity of every neuron) and employ a host of cutting-edge methods (from gene editing to machine learning) to decode how the little worm uses the same neuromodulator chemicals we use to produce appropriate behaviors given its circumstances and internal needs.

For instance, in 2020 Flavell's lab discerned how dopamine allows the worms to solve a problem all organisms face: coordinating multiple motor behaviors (in this case, cruising through a patch of food and laying eggs, as if methodically planting seeds in nutritive soil). And in a series of studies over a decade, Flavell's lab has also built an unprecedentedly comprehensive understanding of how an animal brain employs serotonin, which in people is the most common target for psychiatric drugs. For instance, hungry worms stop and linger when they find a food patch and start eating. Flavell has shown this behavior depends on the neuron NSM emitting serotonin to inhibit neurons that govern locomotion. In the lab's latest paper, published in the journal *Cell* in May, Flavell delineates how each of the worm's six serotonin receptors responds to the chemical both individually and when expressed in combinations in neurons. The study provides a brain-wide mapping of which neurons harbor which combinations of the receptors and uses this knowledge to produce a model that predicts how serotonin release changes brain-wide activity.

"*C. elegans* can't tell us everything, but it has adapted ways to survive and thrive in its natural environment using behavioral strategies that have resemblances to humans. That provides an amazing opportunity for discovery," Flavell said.

Weissbourd had two aims when he pioneered the use of *C. hemisphaerica* jellyfish as a model for systems neuroscience. One was that, like Flavell, he is interested in understanding fundamental, conserved principles of how behavior emerges from a whole nervous system. Though the jellyfish has no central brain, it produces complex behaviors appropriate for its context and its internal states, such as hunger. The jellyfish has several thousand neurons, is also transparent for easy imaging and has a uniquely advantageous life cycle in that its essentially immortal polyps can spawn exact genetic clones daily, Weissbourd said. That enables his lab to grow distinct genetic lines in perpetual abundance. His postdoctoral work focused on establishing methods for genetically engineering the jellyfish so that scientists can use modern research methods and experiments to interrogate how its neuronal activity produces behavior.

Having established this new model (and his new lab at MIT), Weissbourd has many open questions to pursue. Do they use the same neurotransmitters? How are their synapses structured? How do functions like perception and behavior emerge from these underlying properties and the organization of the jellyfish's nervous system?

Diverse and different

If Weissbourd's first aim is to understand the jellyfish's similarities to other animals, the other is focused on understanding the value of how it is divergent. Jellyfish split off from the evolutionary branch that produced humans about 600 million years ago, not long after biologists believe the first nervous systems emerged. Fossils don't preserve neurons, though, so the best way to make inferences about what features emerged in the very first nervous systems is to see what the most evolutionarily divergent organisms nevertheless have in common.

And the ways in which jellyfish outright differ can provide insight into alternative ways that nervous systems can maintain their health. Weissbourd's postdoctoral work documented amazing degrees of regenerative capacity in the jellyfish nervous system. They are constantly adding new neurons so even when he wiped out a whole type of the cells (about 10 percent of its total neurons), the population restored rapidly (since then he's found that the function those neurons enabled was only lost for about a week before the jellyfish rebuilt it).

In the cases when they are similar to us, as well as in the instances when they are very different, tiny model organisms can be enormously informative.

From labs to the streets, experts work to defuse childhood threats to **mental health**

Symposium speakers describe numerous ways to promote prevention, resilience, healing and wellness after early life stresses

Threats to lifelong mental health can arise for young children from sources including poverty, abuse or neglect at home and racism, inequity and pollution outside their doors, but the hopeful message that a range of experts brought to MIT May 11 was that amid these many risks, approaches to provide effective protections and remedies are numerous and growing.

In welcome and closing remarks that framed The Picower Institute for Learning and Memory's daylong symposium, "Environmental and Social Determinants of Child Mental Health," Director and Picower Professor Li-Huei Tsai and School of Science Dean Nergis Mavalvala highlighted how new treatment strategies, programs for prevention, and practices for delivering care are emerging from a continuum that spans fundamental scientific, medical and public health research to evidence-based community services and social activism.

"When we come together to examine the effects of early life stress, toxic environmental exposures, and systemic social inequalities on the mental health of children and the adults they become, it is clear that science—especially neuroscience—has a crucial role to play not only in promoting health, but also in addressing injustice," Tsai said in her introduction. "When adverse childhood experiences undermine mental health, making most every aspect of life so much harder, that is injustice. But when scientists apply their talents and expertise to preventing and reversing those harms, that reduces injustice. Scientists can produce the evidence needed for policy change. Scientists can discover ways to promote resilience and treat mental health problems."

By the end of the day, after 15 talks from neuroscientists, physicians, psychologists, public health researchers and advocates, Mavalvala summarized: "We could never understand specific mechanisms linking early childhood stressors and toxic exposures to problems with mental health if we hadn't first begun with the more fundamental questions about the workings of epigenetics and neural circuitry. And from there we go to planning solutions and we go all the way to activism and social justice. That's the arc by which we change the world."

The Picower Institute jointly arranged the day's program with The JPB Foundation, a philanthropy that supports the Institute and many of the symposium speakers' efforts. Tsai and Mavalvala both thanked JPB President Barbara Picower, who joined remotely from New York with remarks helping to welcome an audience of hundreds of in-person and online attendees.

Discoveries during development

While it's intuitive that a difficult childhood can trouble people for a lifetime, many speakers demonstrated the value of research to discover both the specific mechanisms that connect early life stresses to mental health problems and the molecular means by which some people remain resilient.

Byungkook Lim, for example, described how his lab at UC San Diego has identified a particular class of neurons in a specific area of the brain whose activity becomes altered by a social isolation trauma during development to predispose mice to binge eating and obesity. Intervening to tamp down that activity prevents overeating, he showed. Catherine Peña of Princeton University discussed how brain cells in mice that respond to the acute stress of a temporary maternal separation during early development become more active amid stress later in life because of the way a particular molecule changes their gene expression (an example of epigenetics, or how molecular alterations to DNA change how genes are expressed). But her lab has also found that suppressing reactivation of the cells promotes resilience to those elevated stress responses in adulthood.

Picower Institute Research Scientist and Boston Children's Hospital physician Ravi Raju, who led efforts to organize the symposium, discussed his research in Tsai's lab that has identified a connection between intellectual stimulation early in life and eventual resilience to Alzheimer's disease. He co-led a study showing how raising young mice in enriching environments full of toys and extra space increases the activity of the molecule MEF2, which promotes gene expression that they found both in mice and humans is closely associated with sustained cognitive ability even amid disease pathology.

"With mechanistic understanding of why resilience can be brought about… we can build new repertoires of treatments, we can mobilize interventions in a really evidence-based way," Raju said.

Picower Institute research scientist Ravi Raju speaks about the molecular basis of cognitive resilience. Image by Faith Ninivaggi

Harvard environmental epidemiologist Marc Weisskopf presented evidence that epigenetic effects can transfer across generations. Through reviews of data collected in massive studies of women's health, his lab has shown that smoking among maternal grandmothers significantly increases the odds of autism in grandchildren, even accounting for the mother's smoking. The results suggest that some environmental threats to child mental health are transferred through effects on DNA in germline, or reproductive, cells such as eggs and that health policy

should better consider environmental effects on germline cells.

Brief talks by graduate students and postdocs provided additional insights into brain and epigenetic mechanisms. MIT student Juan Santoyo discussed how studying the brain chemical noradrenaline could lead to the development of non-invasive biomarkers of elevated stress responses in people who've experienced early-life trauma. Fellow student Gabi Drummond described her research on how noradrenaline promotes learning from surprising results, but that early life stress could upset that mechanism. MIT student Alexandra Decker reported her findings that children from households with low socioeconomic status show dampened responses to reward compared to children from more well-off households, another factor that could undermine learning and promote depression. And Harvard postdoc Ran Rotem described his efforts to unravel a linkage between maternal hypothyroidism and increased autism risk among offspring.

Care in communities

While scientific speakers described neurobiological mechanisms through which environmental and social experiences determine mental health, many other speakers discussed efforts to work in communities to shape those experiences for the better via research-based medical, public health, and policy action.

In the symposium's keynote address, Cecile Richards, co-founder of the women's political organization Supermajority and former president of Planned Parenthood, mixed anecdotes about individual women and families with research data, including from a recent Brookings Institution report, to argue that when women gained access to legal, medically safe abortion care that was critical for maternal health and therefore child and household well-being. Since last year's "Dobbs" ruling overturning Roe v. Wade, many states have renewed abortion restrictions. Richards is working to reverse those.

"Access to legal abortion reduced the number of women who were teen mothers by 34 percent and the number who were teen brides by 20 percent," she said. "Abortion legalization reduced maternal mortality among black women by 30 to 40 percent. Access to abortion is also directly related and linked to women's increased education, ability to participate in the workforce and their earnings. Legal abortion reduced cases of child abuse, child neglect, reduced the number of children who live in poverty in America and improved long run outcomes for an entire generation of children by increasing the likelihood that they would attend college and reducing the likelihood of them living in poverty."

In his remarks, Robert Sege of Tufts University School of Medicine highlighted the transformative difference positive childhood experiences (PCEs) can make in the lives of children, even if they've experienced profoundly adverse childhood experiences (ACEs). A study he led showed that among people with four or more ACEs, exposure to 6-7 PCEs reduced the rate of adulthood depression and poor mental health from 60 percent to 20 percent. An organization he leads, Healthy Outcomes from Positive Experiences (HOPE), works to foster PCEs by working alongside families and communities around the country.

University of Connecticut Pediatrician Paul Dworkin described another national program called Help Me Grow. After decades working to treat at-risk children and studying how to improve practices and systems for delivery of effective care, Dworkin founded the organization to help communities better integrate a wide variety of child services and resources so that they can be more easily accessed and become better aligned to family goals. It now operates in 31 states.

Few, if any, communities have experienced more adversity than many Native American nations. In her remarks, Annie Belcourt, a psychologist and chair of Native American studies at the University of Montana, shared how restoration of Blackfeet spiritual ceremonies and experiences has distinct positive effects on mental health, advancing the development of an indigenous cultural resilience termed "Ikaakimaat." Participants in ceremonies were significantly less likely to report depression, for example.

Via a panel discussion, the symposium highlighted another emerging source of positive experiences with direct impacts on mental health: exposure to nature. The panelists—Nsedu Witherspoon of Children's Environmental Health Network, Gregory Bratman of the University of Washington, and Sarah Milligan-Toffler of Children & Nature Network—advocated for municipalities to invest more in greening urban areas, especially schoolyards.

Picower Institute Assistant Professor Sara Prescott (right) moderates a panel discussion among speakers (l. to r.) Sarah Milligan-Toffler, Gregory Bratman and Nsedu Witherspoon. Image by Faith Ninivaggi

Witherspoon referenced research showing how exposures to pollutants during gestation and early childhood can undermine mental health. She described the efforts of CEHN, where she is executive director, to reduce those risks, including advocating for environmental protection policies and training childcare facility owners on how to create healthier, safe environments in their facilities and encouraging them to give kids more opportunities for exposure to nature.

Bratman noted that just as social or personal stresses can make people more susceptible to environmental ones, remedies such as increasing the presence of nature in urban environments might simultaneously improve both problems (for instance, increased urban green spaces can reduce air pollution and improve psychological wellbeing). Bratman described some of his research as director of UW's Environment and Wellbeing Lab to experimentally test and validate such ideas—walks in the park reduced anxiety and rumination and elevated cognition.

Milligan-Toffler said the Children & Nature Network regularly disseminates the latest research on the health benefits of nature exposure and develops programs in 50 communities around the country to increase it and make it more equitable. Working with partners, for instance, the organization is studying integrating nature exposures into social work services provided to children.

"The research really does point to nature being an effective therapeutic intervention when a mental health crisis is present," Milligan-Toffler said.

From fundamental science labs to organizations serving communities and families, speakers said, many ways are emerging to reduce and reverse the harms to young children that could otherwise last a lifetime.

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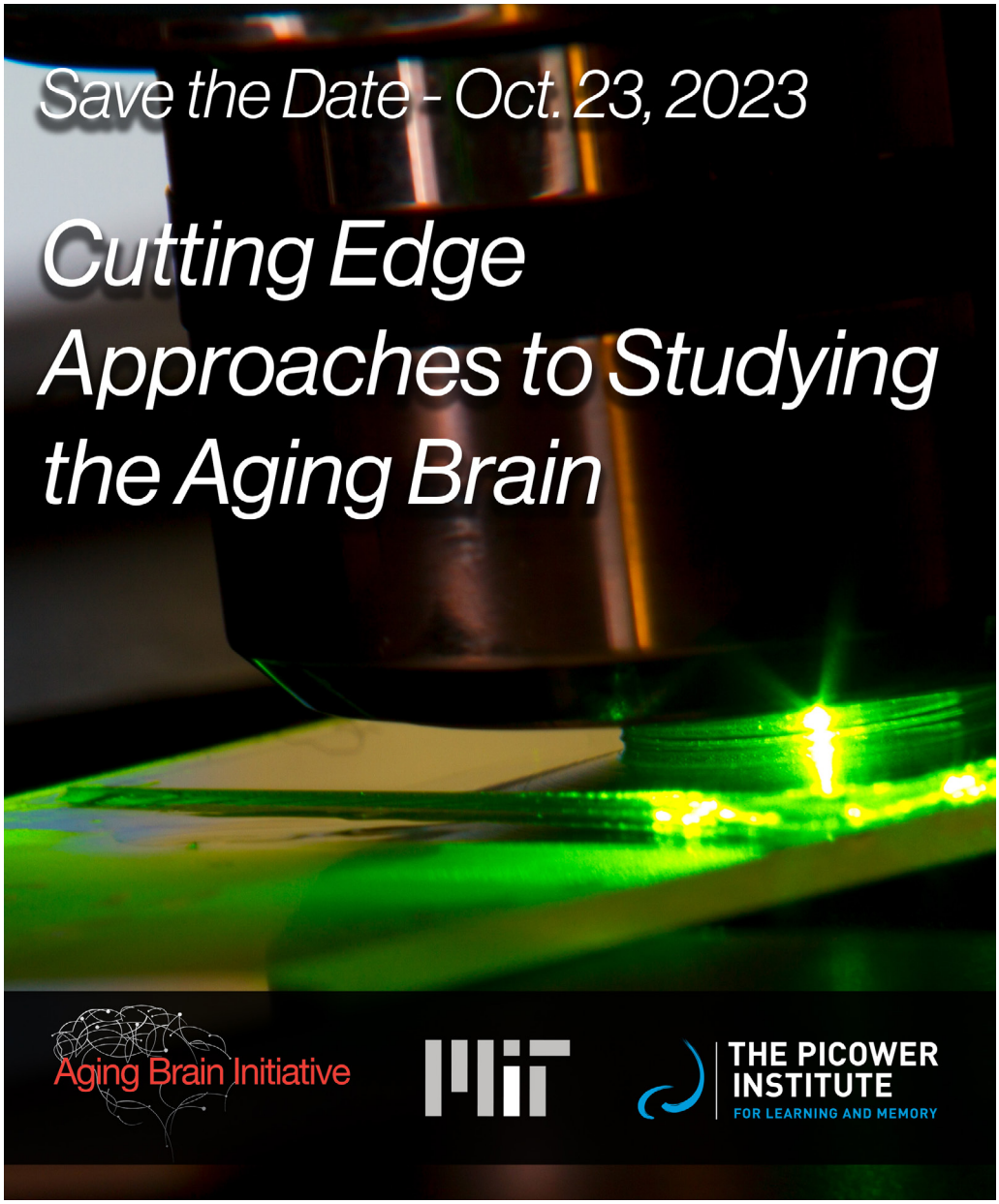

Save the Date: Dec. 11, 2023

The 2023 Picower Lecture with Catherine Dulac, HHMI, Harvard University

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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; **Sara Prescott,** Assistant Professor of 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; **Brady Weissbourd,** Assistant Professor of Biology; **Matthew Wilson**, Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology, Associate Director, The Picower Institute for Learning and Memory.