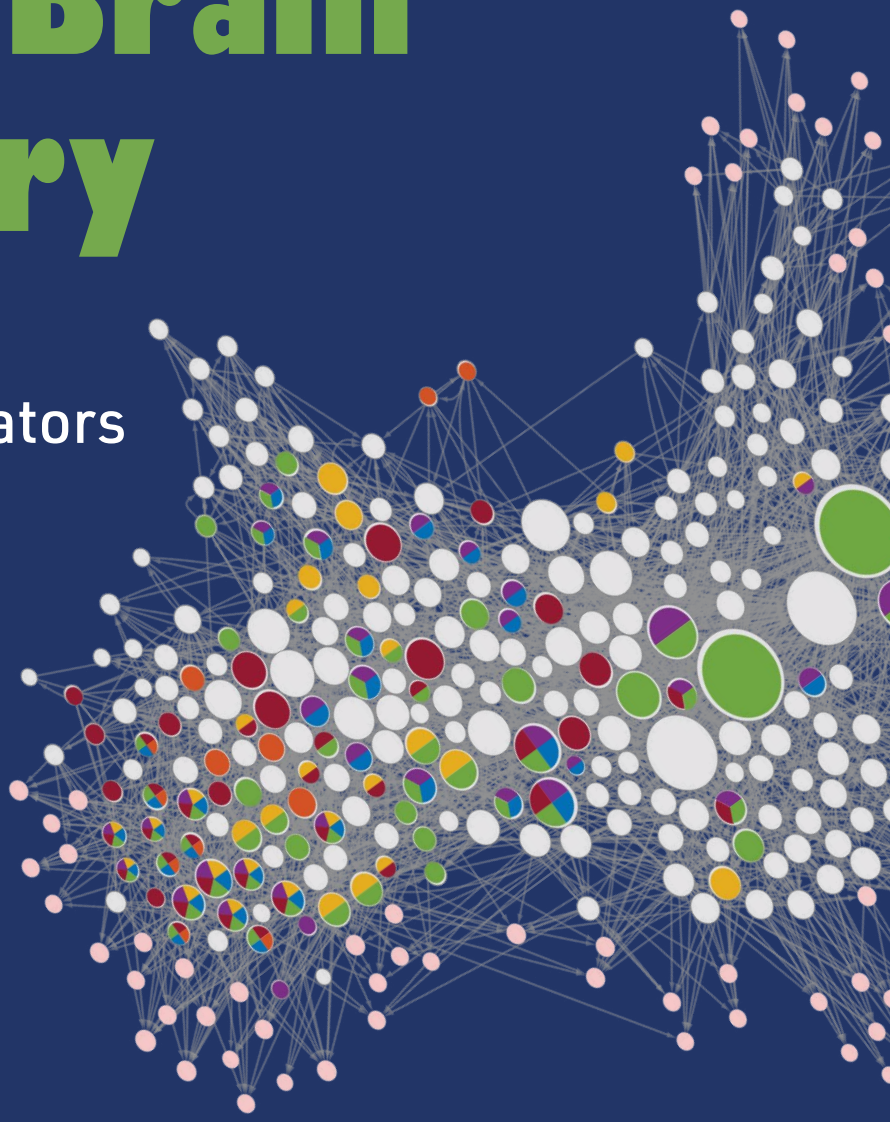
Better Living Through Brain Chemistry



Studying neuromodulators such as serotonin and norepinephrine could help make them better drug targets.

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Neuroscience News

FALL 2024

THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY

DIRECTOR'S **MESSAGE**

Dear Friends,

As scientific disciplines go, neuroscience is young. It's barely more than a century old. That, combined with the incredibly deep complexity of its subject matter means that the potential for discovery is enormous. If that isn't exciting enough, consider how important some of the discoveries yet to me made will be. They could be treatments and cures for neurological and psychiatric diseases. They could be the basis of the next wave of artificial intelligence. They could solve mysteries about how we think, feel, behave and remember.

This issue of *Neuroscience News* is brimming with exciting examples of potential. Our cover story (p. 12) delves into the brain's neuromodulatory chemistry, an ancient and fundamental property targeted (often imprecisely) by many psychiatric, and psychedelic drugs. There are many reasons to study neuromodulators such as serotonin, norepinephrine and endocannabinoids, but among them is that if we understood these complex systems better–if we could mimic the precision that the brain itself has evolved–we could make more effective treatments with fewer side effects for conditions like depression, PTSD and many more.

Another exciting source of potential in the pages that follow come from new advances in our ability to see the brain. No one has ever been able to show it to you the way Kwanghun Chung's lab can (see p. 3). Three key innovations have enabled the ability to visualize entire *in tact* hemispheres of human brains down to the scale of individual proteins and the connections neurons make with each other. This advance opens up the potential for fully mapping the whole human brain in subcellular detail.

Finally, we're brimming with pride about a series of awards that will enable each of our youngest faculty members to make advances of their own (see pp. 7-9). Linlin Fan, Steve Flavell, Sara Prescott and Brady Weissbourd have each earned competitive new honors in the last few months.

It's an exciting time to be here. We're excited to share our potential with you.

LI-HUEI TSAI, DIRECTOR

The Picower Institute for Learning and Memory

Study across 6 brain regions discerns **Alzheimer's** vulnerability and resilience factors

An MIT study in *Nature* provides new evidence for how specific cells and circuits become vulnerable in Alzheimer's disease, and hones in on other factors that may help some people show resilience to cognitive decline, even amid clear signs of disease pathology. To highlight potential targets for interventions to sustain cognition and memory, the authors engaged in a novel comparison of gene expression across multiple brain regions in people with or without Alzheimer's disease, and conducted lab experiments to test and validate their major findings.

Brain cells all have the same DNA but what makes them differ, both in their identity and their activity, are their patterns of how they express those genes. The new analysis measured gene expression differences in more than 1.3 million cells of more than 70 cell types in six brain regions from 48 tissue donors, 26 of whom died with an Alzheimer's diagnosis and 22 of whom without. As such, the study provides a uniquely large, far-ranging and yet detailed accounting of how brain cell activity differs amid Alzheimer's disease by cell type, by brain region, by disease pathology, and by each person's cognitive assessment while still alive.

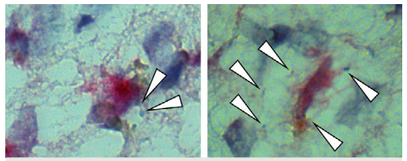
"Specific brain regions are vulnerable in Alzheimer's and there is an important need to understand how these regions or particular cell types are vulnerable," said co-senior author Li-Huei Tsai, Picower Professor of Neuroscience and director of The Picower Institute. "And the brain is not just neurons. It's many other cell types. How these cell types may respond differently, depending on where they are, is something fascinating we are only at the beginning of looking at."

Hansruedi Mathys, Carles Boix, and Leyla Akay led the study analyzing the prefrontal cortex, entorhinal cortex, hippocampus, anterior thalamus, angular gyrus, and the midtemporal cortex. MIT Computer Science Professor Manolis Kellis is the co-senior author.

Some of the earliest signs of amyloid pathology and neuron loss in Alzheimer's occur in memory-focused regions called the hippocampus and the entorhinal cortex. In those regions, and in other parts of the cerebral cortex, the researchers were able to pinpoint a potential reason why. One type of excitatory neuron in the hippocampus and four in the entorhinal cortex were significantly less abundant in people with Alzheimer's than in people without. Individuals with depletion of those cells performed significantly worse on cognitive assessments. Moreover, many vulnerable neurons were interconnected in a common neuronal circuit. And just as importantly, several either directly expressed a protein called Reelin, or were directly affected by Reelin signaling. In all, therefore, the findings distinctly highlight especially vulnerable neurons, whose loss is associated with reduced cognition, that share a neuronal circuit and a molecular pathway.

To find factors that might preserve cognition, even amid pathology, the team examined which genes, in which cells, and in which regions, were most closely associated with cognitive resilience.

Across several brain regions, astrocyte cells that expressed genes associated with antioxidant activity and with choline metabolism and polyamine biosynthesis were significantly associated with sustained cognition, even amid high levels of tau and amyloid pathology. The results reinforced previous research findings led by Tsai and Susan Lundqvist in which they showed the dietary supplement choline helped astrocytes cope with the dysregulation of lipids caused by the most significant Alzheimer's risk gene, the APOE4 variant. The antioxidant findings also pointed to a molecule that can be found as a dietary supplement, spermidine, which may have anti-inflammatory properties, although such an association would need further work to be established causally.



White arrows indicate expression of the gene GPCPD1 (blue) in astrocyte cells (magenta). Expression is higher in people with cognitive resilience to Alzheimer's pathology (right).

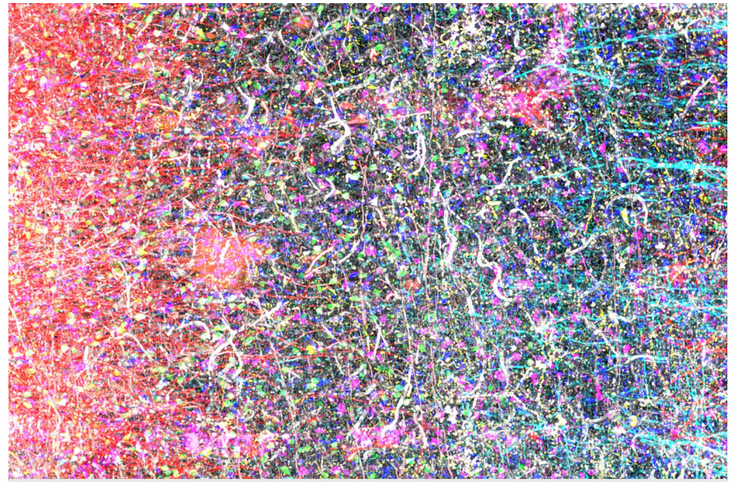
3D imaging of whole human brain hemispheres at subcellular resolution

In a new study in *Science*, an MIT-based team describes a technology pipeline that enabled them to finely process, richly label and sharply image full hemispheres of the brains of two donors—one with Alzheimer's and one without—at high resolution and speed.

"We performed holistic imaging of human brain tissues at multiple resolutions from single synapses to whole brain hemispheres," said senior author Kwanghun Chung, associate professor in The Picower Institute. "This technology pipeline really enables us to analyze the human brain at multiple scales. Potentially this pipeline can be used for fully mapping human brains."

The new study does not already present a comprehensive map or atlas of the entire brain, in which every cell, circuit and protein is identified and analyzed, but with full hemispheric imaging, it demonstrates an integrated suite of three technologies to enable that and other long-sought neuroscience investigations. The research provides a "proof of concept" by showing numerous examples of what the pipeline makes possible, including sweeping landscapes of thousands of neurons within whole brain regions, diverse forests of cells each in individual detail, and tufts of subcellular structures nestled among extracellular molecules. The researchers also present a rich variety of quantitative analytical comparisons focused on a chosen region within the Alzheimer's and non-Alzheimer's hemispheres.

The importance of being able to image whole hemispheres of human brains intact and down to the resolution of individual synapses (the connections that neurons forge to make circuits) is two-fold for understanding the human brain in health and disease, Chung said.



A section of human brain tissue, with 12 colors of labeling simultaneously resolving various cells, vasculature and proteins.

On one hand, it will enable scientists to conduct integrated explorations of questions using the same brain, rather than having to, for example, observe different phenomena in different brains, which can vary significantly, and then trying to construct a composite picture of the whole system. A key feature of the new technology pipeline is that analysis doesn't degrade the tissue. On the contrary, it makes the tissues extremely durable and repeatedly re-labelable to highlight different cells or molecules as needed for new studies for potentially years on end. In the paper, Chung's team demonstrates using 20 different antibody labels to highlight distinct cells and proteins but they are already expanding that to a hundred or more.

On the other hand, the pipeline's relatively high scalability and throughput (imaging a whole brain hemisphere once it is prepared takes 100 hours rather than many months) means that it is possible to create many samples to represent different sexes, ages, disease states and other factors that can enable robust comparisons with increased statistical power. Chung said he envisions creating a brain bank of fully imaged brains that researchers could analyze and re-label as needed for new studies.

Chung said the biggest challenge he faced in achieving the advances described in the paper was building a team at MIT that included three especially talented young scientists, each a co-lead author of the paper because of their key roles in producing the three major innovations. Ji Wang, a mechanical engineer and former postdoc, developed the "Megatome," a device for slicing intact human brain hemispheres so finely that there is no damage. Juhyuk Park, a materials engineer and former postdoc, developed the chemistry that makes each brain slice clear, flexible, durable, expandable, and quickly, evenly and repeatedly labelable—a technology called "mELAST." Webster Guan, a former MIT chemical engineering graduate student with a knack for software development, created a computational system called "UNSLICE" that can seamlessly reunify the slices to reconstruct each hemisphere in full 3D down to the precise alignment of individual blood vessels and neural axons (the long strands they extend to forge connections with other neurons).

For years Chung has also collaborated with co-author Matthew Frosch, an Alzheimer's researcher and director of the brain bank at Massachusetts General Hospital, to image and understand Alzheimer's disease brains. With the new pipeline established they began an open-ended exploration, first noticing where within a slab of tissue they saw the greatest loss of neurons in the disease sample compared to the control. From there, they followed their curiosity—as the technology allowed them to do—ultimately producing a series of detailed investigations described in the paper.

"This pipeline allows us to have almost unlimited access to the tissue," Chung said. "We can always go back and look at something new."

Study helps explain how **anesthesia** drug induces unconsciousness

Using a novel technique for analyzing neuron activity, MIT researchers have discovered that the drug propofol induces unconsciousness by disrupting the brain's normal balance between stability and excitability. The drug causes brain activity to become increasingly unstable, until the brain loses consciousness.

"The brain has to operate on this knife's edge between excitability and chaos. It's got to be excitable enough for its neurons to influence one another, but if it gets too excitable, it spins off into chaos. Propofol seems to disrupt the mechanisms that keep the brain in that narrow operating range," says Earl K. Miller, Picower Professor in The Picower Institute.

The new findings, reported in *Neuron*, could help researchers develop better tools for monitoring patients as they undergo general anesthesia.

Miller and Ila Fiete, professor in Brain and Cognitive Sciences and The McGovern Institute, are the senior authors of the new study. MIT graduate student Adam Eisen and MIT postdoc Leo Kozachkov are the lead authors of the paper.

Propofol binds to GABA receptors, inhibiting neurons that have them. Other anesthesia drugs act on different types of receptors, and the mechanism for how all of these drugs produce unconsciousness is not fully understood.

The team hypothesized that propofol, and possibly other anesthesia drugs, interfere with a brain state known as "dynamic stability." In this state, neurons have enough excitability to respond to new input, but the brain is able to quickly regain control and prevent them from becoming overly excited.

Previous studies of how anesthesia drugs affect this balance have found conflicting results: Some suggested that during anesthesia, the brain shifts toward becoming too stable and unresponsive, which leads to loss of consciousness. Others found that the brain becomes too excitable, leading to a chaotic state that results in unconsciousness.

Part of the reason for these conflicting results is that it has been difficult to accurately measure dynamic stability in the brain. Measuring dynamic stability as consciousness is lost would help researchers determine if unconsciousness results from too much stability or too little stability.

In this study, the researchers analyzed electrical recordings made in the brains of animals that received propofol over an hour-long period, during which they gradually lost consciousness. The recordings were made in four areas of the brain that are involved in vision, sound processing, spatial awareness, and executive function.

These recordings covered only a tiny fraction of the brain's overall activity, so to overcome that, the researchers used a technique called delay embedding. This technique allows researchers to characterize dynamical systems from limited measurements by augmenting each measurement with measurements that were recorded previously.

Using this method, the researchers were able to quantify how the brain responds to sensory inputs, such as sounds, or to spontaneous perturbations of neural activity.

In the normal, awake state, neural activity spikes after any input, then returns to its baseline activity level. However, once propofol dosing began, the brain started taking longer to return to its baseline after these inputs, remaining in an overly excited state. This effect became more and more pronounced until the animals lost consciousness.

This suggests that propofol's inhibition of neuron activity leads to escalating instability, which causes the brain to lose consciousness, the researchers say.

As Fiete explains, "This paradoxical effect, in which boosting inhibition destabilizes the network rather than silencing or stabilizing it, occurs because of disinhibition. When propofol boosts the inhibitory drive, this drive inhibits other inhibitory neurons, and the result is an overall increase in brain activity."

The researchers suspect that other anesthetic drugs, which act on different types of neurons and receptors, may converge on the same effect through different mechanisms — a possibility that they are now exploring.

If this turns out to be true, it could be helpful to the researchers' ongoing efforts to develop ways to more precisely control the level of anesthesia that a patient is experiencing. These systems, which Miller is working on with Edward Hood Taplin Professor Emery N. Brown, work by measuring the brain's dynamics and then adjusting drug dosages accordingly, in real-time.

"If you find common mechanisms at work across different anesthetics, you can make them all safer by tweaking a few knobs, instead of having to develop safety protocols for all the different anesthetics one at a time," Miller says. "You don't want a different system for every anesthetic they're going to use in the operating room. You want one that'll do it all."

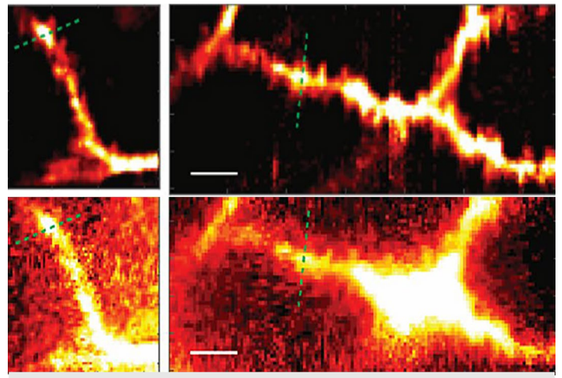
The researchers also plan to apply their technique for measuring dynamic stability to other brain states, including neuropsychiatric disorders.

Microscope sharpens view of circuit connections

The brain's ability to learn comes from "plasticity," in which neurons constantly edit and remodel the connections called synapses that they make with other neurons to form circuits. To study plasticity, neuroscientists seek to track it at high resolution across whole cells, but plasticity doesn't wait for slow microscopes to keep pace and brain tissue is notorious for scattering light and making images fuzzy. In a paper in *Scientific Reports*, a collaboration of MIT engineers and neuroscientists describes a new microscopy system designed for faster, clearer, and more frequent imaging of the living brain.

The system, called "multiline orthogonal scanning temporal focusing" (mosTF), works by scanning brain tissue with lines of light in perpendicular directions. The new system proved in the team's tests to be eight times faster than a two-photon scope that goes point by point, and proved to have a four-fold better signal to background ratio (a measure of the resulting image clarity) than a two-photon system that just scans in one direction.

"Tracking rapid changes in circuit structure in the context of the living brain remains a challenge," said co-author Elly Nedivi, William R and Linda Young Professor in The Picower Institute. "The mosTF system significantly reduces scan time without sacrificing resolution."



Neural dendrites imaged with mosTF (top) are more sharply resolved than the same neuron imaged with a single-direction line scan (bottom).

Scanning a whole line of a sample is inherently faster than just scanning one point at a time, but it kicks up a lot of scattering. Newer scopes produce a stronger signal (thereby resolving smaller and fainter features of stimulated neurons) by algorithmically reassigning scattered photons back to their origin. In a two-dimensional image, that process is better accomplished by using the information produced by a two-dimensional, perpendicular-direction system such as mosTF, than by a one-dimensional, single-direction system, said lead author Yi Xue.

In the study the team, which also included MIT Mechanical Engineering Professor Peter T.C. So, used mosTF to image neurons in the brain of a live, anesthetized mouse and compared it to a single-direction system. The mosTF scope achieved a four-fold better signal-to-background ratio and was able to reveal the spines that protrude along the vine-like processes, or dendrites, that grow out of the neuron cell body. Monitoring plasticity requires being able to watch those spines grow, shrink, come and go across the entire cell, Nedivi said.

Novel sensor improves imaging of neural activity

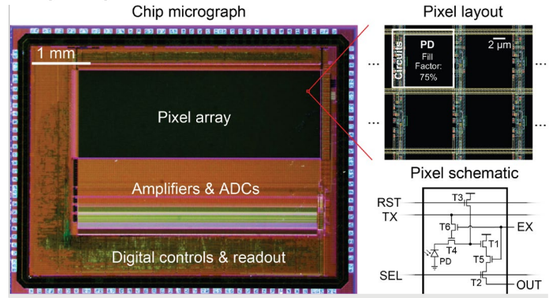
Neurons communicate electrically so to understand how they produce brain functions such as memory, neuroscientists must track how their voltage changes—sometimes subtly—on the timescale of milliseconds. In a new paper in *Nature Communications*, MIT researchers describe a novel image sensor with the capability to substantially increase that ability.

The invention led by Jie Zhang, a postdoctoral scholar in The Picower Institute lab of Sherman Fairchild Professor Matt Wilson, is a new take on the standard "CMOS" technology used in scientific imaging. In that standard approach, all pixels turn on and off at the same time—a configuration with an inherent trade-off in which fast sampling means capturing less light. The new chip enables each pixel's timing to be controlled individually. That arrangement provides a "best of both worlds" in which neighboring pixels can essentially complement each other to capture all the available light without sacrificing speed.

In experiments described in the study, Zhang and Wilson's team demonstrates how "pixelwise" programmability enabled them to improve visualization of neural voltage "spikes," which are the signals neurons use to communicate with each other, and even the more subtle, momentary fluctuations in their voltage that constantly occur between those spiking events.

"Measuring with single-spike resolution is really important as part of our research approach," said senior author Wilson, whose lab studies how the brain encodes and refines spatial memories both during wakeful exploration and during sleep. "Thinking about the encoding processes within the brain, single spikes and the timing of those spikes is important in understanding how the brain processes information."

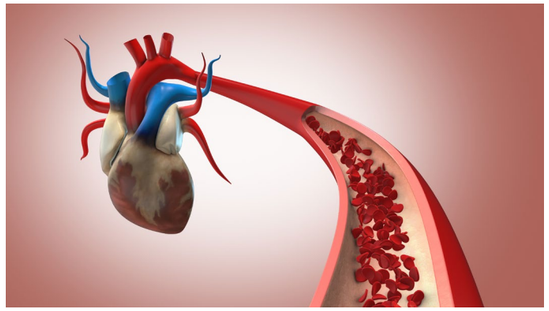
In two key sets of experiments described in the paper, the team showed head-to-head how their pixelwise chip improved voltage imaging compared to a traditional CMOS camera. In each set different manipulations of individual pixel timing allowed them to gather more light without sacrificing imaging speed, and to capture a wider range of faster and slower voltage changes.



The left side shows the whole imaging chip micrograph, while the right side displays the pixel layout.

Method estimates cardiovascular state for better blood pressure management

If patients receiving intensive care or undergoing major surgery develop excessively high or low blood pressures, they could suffer severe organ dysfunction. It's not enough for their care team to know that pressure is abnormal. To choose the correct drug to treat the problem, doctors must know *why* blood pressure has changed. A new MIT study presents the mathematical framework needed to derive that crucial information accurately and in real time.



The mathematical approach, described in a recent study in *IEEE Transactions on Biomedical Engineering*, produces proportional estimates of the two critical factors underlying blood pressure changes: the heart's rate of blood output (cardiac output) and the arterial system's resistance to that blood flow (systemic vascular resistance). By applying the new method to previously collected data from animal models, the researchers show that their estimates, derived from minimally invasive measures of peripheral arterial blood pressure, accurately matched estimates using additional information from an invasive flow probe placed on the aorta. Moreover, the estimates accurately tracked the changes induced in the animals by the various drugs physicians use to correct aberrant blood pressure.

"Estimates of resistance and cardiac output from our approach provide information that can readily be used to guide hemodynamic management decisions in real time," the study authors wrote.

With further testing leading to regulatory approval, the authors said, the method would be applicable during heart surgeries, liver transplants, intensive care unit treatment and many other procedures affecting cardiovascular function or blood volume.

"Any patient who is having cardiac surgery could need this," said study senior author Emery N. Brown, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience in The Picower Institute. Brown is also an anesthesiologist at Massachusetts General Hospital. "So might any patient undergoing a more normal surgery but who might have a compromised cardiovascular system such as ischemic heart disease. You can't have the blood pressure being all over the place."

The study's lead author is electrical engineering and computer science (EECS) graduate student Taylor Baum, who is co-supervised by Brown and Munther Dahleh, William A. Coolidge Professor in electrical engineering and computer science.

Model of ketamine's molecular action predicts effects on the brain

Ketamine is widely used at varying doses for sedation, pain control, general anesthesia and as a therapy for treatment-resistant depression. While scientists know its target in brain cells and have observed how it affects brain-wide activity, they haven't known entirely how the two are connected. A new study used computational modeling of previously unappreciated physiological details to fill that gap and offer new insights into how ketamine works.

"This modeling work has helped decipher likely mechanisms through which ketamine produces altered arousal states as well as its therapeutic benefits for treating depression," said co-senior author Emery N. Brown, Edward Hood Taplin Professor of Computational Neuroscience and Medical Engineering at The Picower Institute.

Led by Elie Adam, researchers from MIT, Boston University, Massachusetts General Hospital and Harvard said the predictions of their model, published in *Proceedings of the National Academy of Sciences*, could help physicians make better use of the drug.

The core advance of the study involved biophysically modeling what happens when ketamine blocks the "NMDA" receptors in the brain's cortex. With their biophysical model, the scientists simulated how different doses of ketamine affecting NMDA receptors would alter the activity of a model brain network.

The team's simulations successfully recapitulated the real brain waves that have been measured via EEG electrodes on the scalp of a human volunteer who received various ketamine doses and the neural spiking that has been measured in similarly treated animals that had implanted electrode arrays. At low doses, ketamine increased brain wave power in the fast gamma frequency range (30-40 Hz). At the higher doses that cause unconsciousness, those gamma waves became periodically interrupted by "down" states where only very slow frequency delta waves occur.

A prediction from the model might help explain how ketamine exerts its antidepressant effects. It suggests that the increased gamma activity of ketamine could entrain gamma activity among neurons expressing a peptide called VIP. This peptide has been found to have health promoting effects, such as reducing inflammation, that last much longer than ketamine's effects on NMDA receptors. The research team proposes that the entrainment of these neurons under ketamine could increase the release of the beneficial peptide, as observed when these cells are stimulated in experiments. This also hints at therapeutic features of ketamine that may go beyond anti-depressant effects. The research team acknowledges, however, that this connection is speculative and awaits specific experimental validation.

HHMI honor will advance studies of internal brain states

The things we do for love. The mistakes we make when we're tired or rushed. The angry words we wish we could take back. The times we jump for joy.

The episodes when our internal emotions and motivations affect our behavior provide some of our strongest and most personal experiences with our selves. But as intensely felt as these times and underlying states can be, they have been difficult for neuroscientists to define and explain. Related disorders such as depression can therefore be harder to treat. Associate Professor Steve Flavell directs a research program in a simple organism, the roundworm *C. elegans*, that he hopes will prove foundational to building an understanding of how internal states arise and influence behavior in nervous systems in general.

"I think that it should be possible to define the basis of internal states in *C. elegans* in concrete terms," Flavell said. "If we can build a thread of understanding from the molecular architecture of neuromodulatory systems, to changes in brain-wide activity, to state-dependent changes in behavior, then I think we'll be in a much better place as a field to think about the basis of brain states in more complex animals."

The long-term impact would not only be a better understanding of the link between brain activity and behavior, but also improved interventions for psychiatric disorders.

These goals have guided Flavell's lab in The Picower Institute ever since he established it in 2016, but as a newly named HHMI Investigator, he will have long-term, flexible support to address the full set of scientific challenges necessary to answer these questions. HHMI's "people, not projects" approach provides investigators with generous, renewable funding that provides the flexibility to let investigators go where ever their scientific questions take them.

C. elegans is simple enough to be studied from the molecular to whole-brain scale, but deceptively complex nonetheless. Though the entire connectome, or wiring diagram, among its 302 neurons has been fully mapped and its genes are readily manipulable in lab experiments, the worm nevertheless displays a remarkable array of flexible behaviors that often employ the same molecular machinery found in humans, including neuromodulatory chemicals such as serotonin and dopamine. In all, the worm has more than 100 different neuromodulators that might enable its internal states to change how it behaves.

In two papers last year, Flavell's lab blended techniques ranging from genetic and molecular manipulations, to imaging of behavior and brain-wide neural activity, to computational modeling to produce major brain-wide insights. In one study, the team built a model that can predict how a majority of the worm's neurons encode and represent its behaviors, and found that about 30 percent of the worm's neurons remain flexible to account for different behavioral situations. In another paper the scientists thoroughly mapped the worm's six distinct serotonin receptors across each neuron in its brain, and showed how serotonin release acts on each of them to affect feeding and locomotion.

One of the main new thrusts of the lab's work, Flavell said, will be to build on those achievements by constructing a new generation of computational models that predict how every neuron responds to a wider range of internal states in the worm.

Another new area of work will delve deeper into how neuromodulators affect the animal's internal states, ranging from studies of how these chemicals are released and diffuse to reach their targets and studies of how they act in combination, Flavell said.

A third major initiative in the lab will tackle the question of how specific features of the connectome – aspects of nervous system wiring – control internal states.

The HHMI award's support doesn't just open up these new opportunities for Flavell, but for his whole lab. As a team of postdocs, graduate students, technicians and other trainees, Flavell said, his lab will now have greater flexibility to consider the biggest questions and implications of their results and to take whatever approaches are needed to investigate them.

In that spirit, as Flavell reflected on being named an HHMI Investigator, which is one of the most prestigious honors in life sciences research, he said he thought of the many contributions former and current members of his lab have made over the years.

"Many of my scientific heroes are HHMI Investigators," Flavell said. "The idea of being included in that group is humbling. But my main reaction is that I just feel extraordinarily proud of the current and former members of my lab. This is really their achievement."

Pew award will fund study of neural role in respiratory disease

On the front lines of exposure to the rest of the world, the body's airways are confronted by dangers ranging from air pollution to allergens to mis-swallowed coffee. To cope, they have defensive reflexes, such as coughing, and repair responses that marshal stem cells to remodel damaged tissue. But in many diseases, such as asthma and chronic obstructive pulmonary disorder (COPD), the lungs' remodeling responses go awry causing serious and even fatal impairments to breathing.

While such diseases and their impact are well known, what is much less clear is how these remodeling responses are triggered, coordinated and resolved. With a new Pew Biomedical Scholar Award from the Pew Charitable Trusts, Sara Prescott, assistant professor in the Department of Biology and The Picower Institute, will test the hypothesis that various types of neurons in the airways are central players in both healthy and pathological remodeling.

"In barrier tissues such as our lungs, neurons serve as sentinels where they're detecting the earliest signs of airway damage and sending that information back to the brain to trigger protective reflexes," Prescott said. "But these neurons are also present at the right places and sensing the same irritants and hazards that cause remodeling. It seems like they are strategically placed in such a way that they're poised to communicate the insult to the tissue. And yet because it has been historically very challenging to selectively access these neurons experimentally, people have largely ignored their role in these diseases. They're often just thought of as bystanders and we want to challenge that assumption."

Prescott has been studying and characterizing airway neurons stemming from the vagus nerve for years. She has also begun investigating other neuron types, like sympathetic innervation of the airways. With the Pew award's support of $300,000 over four years, Prescott and her lab members will apply that knowledge and new techniques her lab has developed to conduct experiments with mice that will test the role of neurons in coordinating airway stem cell remodeling. These will include selectively stimulating different neuron types that innervate the airway to see if that drives different remodeling responses. The lab will also test whether taking these neurons offline will hinder remodeling mechanisms in animals exposed to respiratory insults. In a third set of experiments, Prescott's team will put airway stem cells in a dish and expose them to various factors emitted by airway neurons to see which ones appear to stimulate stem cell remodeling responses.

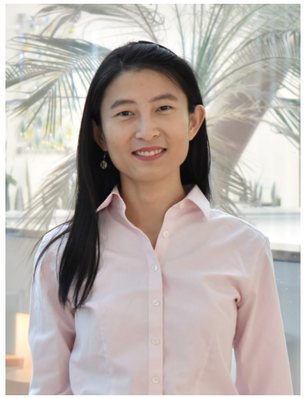
Fellowship enables study of how the brain makes memories of places

With a new fellowship award from the Klingenstein-Simons Foundation, Assistant Professor Linlin Fan will launch research to advance understanding of how the brain employs "plasticity," a term for how neurons change the strength of their circuit connections with other neurons, to learn places.

The study may have medical implications. Because the dynamic she's studying involves endocannabinoids, a brain chemical that can modulate the neurotransmitter release of neurons, the research could shed light on epilepsy and on marijuana use, Fan said. Epileptic seizures are believed to increase endocannabinoid release, which could affect plasticity processes that depend on its levels. Meanwhile, marijuana use supplies the brain with external cannabinoids that could compete with the natural cannabinoid dynamics necessary for place memory plasticity.

There is mounting evidence that place cells, which encode memories of locations, must suppress inhibitory input from fellow neurons to improve their tuning to a favored location. Earlier this year in *Science*, Fan and her colleagues investigated this process, called "depolarization-induced suppression of inhibition" (DSI). They showed that when a place cell receives the excitation that tunes it to a location, it emits an endocannabinoid signal that is received by inhibitory neurons that normally tamp down the place cell's electrical activity. Using Fan's innovative optical methods for analyzing neural electrical activity, they further showed that a cell was able to suppress incoming inhibition when it was receiving excitation, but not when it wasn't. In another experiment they showed that if they knocked out the inhibitory cells' endocannabinoid receptors then the place cells did a poorer job of representing the favored location.

With the Klingenstein-Simons award, Fan plans to more deeply study the role of this inhibitory plasticity in learning and memory.



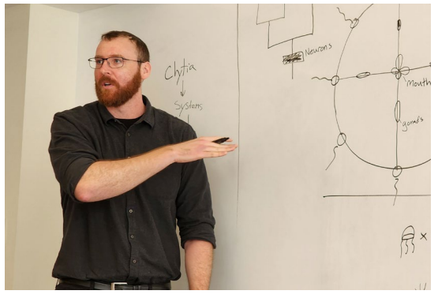
For instance, Fan plans to conduct experiments to test whether excitatory behavioral timescale plasticity (the process that imprints a memory in a place cell) recruits DSI.

"We hypothesize that DSI may promote cellular excitability and open a time window for excitatory synaptic plasticity to occur," Fan said.

To get at whether endocannabinoids have a causal role in modulating inhibition, Fan will knock out the inhibitory cells' endocannabinoid receptors and measure whether the place cells fail to show the same implementation of plasticity they can achieve when cannabinoid signaling is not disrupted. She'll also measure the effect on plasticity when she intervenes to suppress or excite the inhibitory cells.

Searle honor enables study of an organism that constantly adds new neurons

Scientists who dream of a future in which regenerative medicine has advanced enough to enable repairs in human nervous systems currently have more questions than answers. As a recently named Searle Scholar, Assistant Professor Brady Weissbourd will seek to learn some of the needed fundamentals by studying a master of neural regeneration: the jellyfish, *Clytia hemisphaerica*.



Weissbourd has helped to pioneer use of the seafaring species in neuroscience research for many reasons. But what Weissbourd didn't appreciate until he began experimenting with the jellyfish was that they are also incredibly good at refreshing and rebuilding their nervous systems with new cells. After becoming the first researcher to develop the ability to genetically manipulate the organism, he started teasing out how its highly distributed nervous system (there is no central brain), was organized to enable its many behaviors. When he ablated a subnetwork of cells to test whether it was indeed responsible for a particular feeding behavior, he found that within a week it had completely regrown. Moreover, he has observed that the jellyfish constantly produce and integrate new cells, even in the absence of major injury.

The finding raised many questions that his support from the Searle Scholars Program will help him pursue.

"Where are these newborn neurons coming from in both the normal and regenerative contexts?" Weissbourd asked. "What rules guide them to the correct locations to rebuild these networks, both to integrate these newborn neurons into the network without messing it up and also to recreate it during regeneration? Are the rules the same or different between these contexts?"

Additionally, Weissbourd's lab has discerned that within their web-like mesh of neurons, jellyfish harbor more than a dozen different functional subnetworks that enable its variety of different behaviors. He plans to study how regeneration plays out in each, because there may be important differences.

"The ability to understand how nervous systems regenerate has significant implications for regenerative medicine," Weissbourd said.

As part of the new award, Weissbourd also plans to work with collaborator Jeff Lichtman, a professor of molecular and cellular biology at Harvard University, to create a complete 3D reconstruction of a jellyfish's nervous system at the subcellular resolution enabled by electron microscopy.

HHMI supports student's work to advance Alzheimer's research and equity

Alzheimer's disease (AD) is a clear and urgent national health and research priority but for millions of Americans, including MIT graduate student Mingus Rae Zoller, it's also a deeply personal one. With a new Gilliam fellowship funded by the Howard Hughes Medical Institute, Zoller will have support to advance understanding of the neurodegenerative disease that has unexpectedly afflicted her father.

"This is the biggest mystery of my life. How did my Dad get AD?" Zoller said. "If I can contribute one tiny bit of information to explain how AD progresses or how someone could get it, that would be personally fulfilling. That's a big driving force for me."

The Gilliam fellowship also taps into other deep sources of motivation for Zoller. It not only supports her research but also provides her and her adviser Li-Huei Tsai, Picower Professor in The Picower Institute, with resources to promote diversity, equity and inclusion in the sciences. That intersects both with Zoller's enthusiasm for promoting their value in science and her awareness of the particularly difficult challenges that neurodegenerative disease can pose among already disadvantaged populations, such as finding adequate healthcare when money is tight.

Since 2016 Tsai's lab has been finding that increasing the power and synchrony of 40Hz gamma frequency neural activity can reduce Alzheimer's pathology and symptoms. Currently in her second year of graduate study, Zoller is tackling a set of questions raised by these results including how 40Hz stimulation may affect various immune cell types in the brain and its surrounding tissues.

Zoller said she is finding many opportunities at MIT to act on her passion for promoting equity and inclusion in science.

"Taking part in the Brain and Cognitive Sciences Application Assistance Program and the Women+ of Color Project, enabled me to assist dozens of scientists from underserved backgrounds in honing their academic writing skills and crafting compelling statements of purpose for their graduate applications," Zoller said. "I am also a Diversity Ambassador for my graduate program and the DEIJ representative for my lab. I plan to expand my mentorship efforts through MIT programs aimed at supporting under-served minorities such as the research scholars post-bac program and LEAH Knox Scholars Program."

Picower retreats advance science by giving researchers a chance to step back from the lab

Every year members of The Picower Institute find they can explore new ideas and interactions by experiencing the change of scenery afforded by the Dana and Betty Fisher retreat.

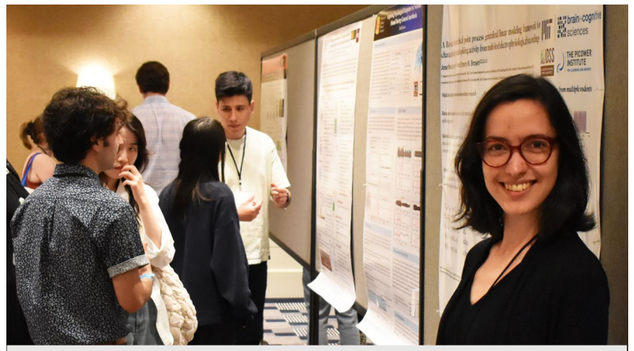
Sometimes the best way for researchers to advance their science is to take a break from their day-to-day, heads-down focus for a change of scenery that enables new ways of thinking and interacting with colleagues. The annual Dana and Betty Fisher Retreat is the step back that helps scientists in The Picower Institute move forward.

"The retreat is literally getting off campus so that everyone is closer together and there are no distractions. All you have is one another. It's a substrate for relaxed, informal discussions," said Picower Professor Mark Bear. "It's really a central part of the intellectual life of The Picower Institute."

Held in late spring along the Massachusetts coast, the retreat blends professional opportunities such as talks about research and careers with social activities such as beach volleyball and karaoke. Freed from their benches and desks, researchers can hear from and interact with colleagues from other labs whom they might not see much in Cambridge.

As one Picower Institute member said in a survey after this year's retreat June 4-5 in Gloucester: "The retreat is where I meet most of the people outside my work area."

Since 2014 retreats have alternated between being Picower-only, like this year's, or combined with those of the Department of Brain and Cognitive Sciences and the McGovern Institute for Brain Research, like last year's in North Falmouth.



Graduate student Josefina Correa Menéndez, at the 2024 retreat poster session

An opportunity ensured

The retreat got its name back in 2008 when the tradition, begun by the Institute's founding director Picower Professor Susumu Tonegawa, needed an enduring source of funding. That came after a fortuitous meeting of minds between Bear, then The Picower Institute's director, and Wendy Fisher.

Betty and Dana Fisher. Image courtesy of Wendy Fisher.

Fisher was seeking to honor the legacy of her parents, Dana and Betty, by distributing charitable funds they had left for her to manage. When they met in Cairo, Egypt, Dana worked for Trans World Airlines, and Betty worked for Life Magazine. They raised Wendy and her siblings on the family's farm in California's Palo Verde Valley. Betty spoke often and passionately of her love of languages (she knew seven) and the explanatory power of the natural sciences, especially chemistry, which she studied at Wellesley College. Dana was fascinated by the scientific study of the mind and human behavior, and greatly valued the scientific method, putting the latest technologies to use in modernizing the farm. Wendy said they valued education, health and science above all. Wendy's own experiences confirmed the value of collaborative, interdisciplinary approaches to problem solving and research.

When Betty died, a trust provided money for Wendy to donate to carry on their values. Amid her research on where to best make the donation, she visited Cambridge. She had met with various organizations and institutions, trying to find where her parents' interest in education might also further research into Alzheimer's--her multilingual mother had become unable to reliably communicate in any language due to the disease. The Picower Institute, where memory and Alzheimer's studies are prominent, merited a visit.

At the time of Fisher's visit, Bear had made fomenting collaboration at the Institute a top priority and was focused on ensuring the retreat's continuation. He and Fisher met and over the course of a few conversations that they each recall fondly, created an endowment for the Dana and Betty Fisher annual retreat that has become a fixture of The Picower Institute.

"I was so grateful," Bear said. "The timing could not have been more perfect. The whole thing was in jeopardy and this saved it."

Fisher said it represented a perfect match in supporting extracurricular educational experiences, and hoped it would foster stimulating scientific conversations, collaboration and research into Alzheimer's.

Fisher said she is certain that her parents would be delighted that top scientists meet others in their community outside of their normal environment. The intent was to enhance the potential for informal conversations and lasting relationships that lead to unexpected connections and, in turn, to breakthrough research into the brain and its afflictions.

Valuable in many ways

Every retreat's program is different, but they each involve a mix of scientific, professional and social activities. At poster sessions, postdocs, graduate students and other researchers can present research in progress and get feedback from colleagues who visit. Retreats frequently include science talks, sometimes from institute trainees and sometimes from guest speakers, and this year featured panels of faculty or other experts discussing science careers or other professional practices and issues.

Picower Institute researchers line up and converse during a speed networking session

Anjanet Loon, technical associate in the lab of Institute director and Picower Professor Li-Huei Tsai, said she drew inspiration from the faculty talks.

"Receiving advice and life stories from Picower's professors felt like a unique privilege, offering early-career individuals like myself invaluable insights and relatable experiences," she said. "Their openness about the difficulties and joys of their journeys resonated with me, and reflecting on their experiences broadened my perspective on how challenge and uncertainty can actually be foundational to innovation and success."

Among the faculty who spoke was Menicon Professor Troy Littleton, who said retreats provide many benefits.

"The Picower summer retreat enables lab members to present their research in a professional setting and to interact with other Picower labs to get input," Littleton said. "The informal nature of the retreat structure also provides plenty of time for inter-lab bonding that plays an important role in enhancing lab morale. Moreover, the ability of lab members to learn more about the ongoing research in other Picower labs facilitates both future collaborations, while providing insights into state-of-the-art neuroscience methodology that could be adapted by our lab down the road."

This year's retreat featured a "speed networking" session in which participants could discuss each other's research and discover shared interests before "rotating" to talk to new partners. At the end, several pairs reported out their favorite findings. For example, even though Loon has spoken about lab techniques before with Prachi Ojha, a postdoc in the lab of Newton Professor Mriganka Sur, speed networking gave her the chance to learn about a particular scientific interest they share: the dysfunction of cells called astrocytes in disease. Loon is interested in the cells in the context of Alzheimer's disease so she said she enjoyed hearing about how Ojha studies them in Rett syndrome.

"Over the years I feel that the retreats have been part of what makes MIT special," Loon said. "The retreats not only allow us to showcase and learn about some of our incredible research, but also foster a community where collaboration and connection thrive. To me, the Picower retreat is a reminder that working together as researchers is as much about the science as it is about supporting each other and growing together. I left feeling inspired and more connected to the brilliant minds around me."

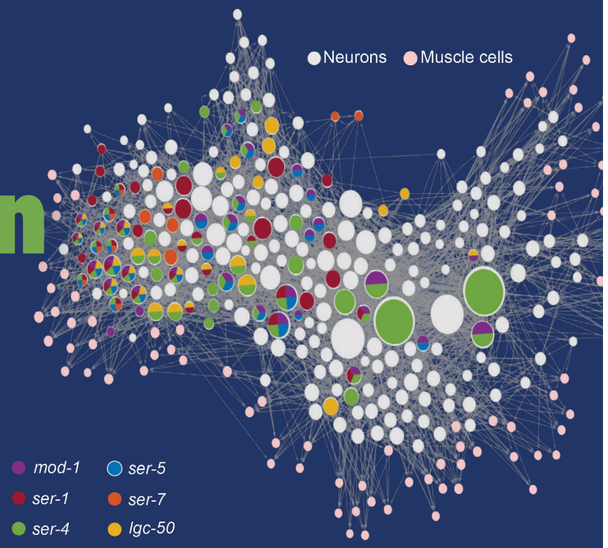
Josefina Correa Menéndez, a PhD candidate in Edward Hood Taplin Professor Emery N. Brown's lab, expressed a similar sentiment. Menendez gave a talk last year and presented a poster this year describing her development of a model for improving the statistical analysis of recordings of neural electrical activity by integrating insights from multiple levels of measurement. For Menéndez, the retreat is an opportunity to learn how her model could be applied by fellow scientists.

"I gained new perspectives on the impact of my work by talking with researchers working in different fields," Menéndez said. "As someone who works on statistical model building and signal processing tools, it is immensely valuable to learn how my work could benefit experimentalists optimally. These opportunities have provided the space for me to do that."

While presenters benefit from feedback, everyone who visits their poster or hears their talk can get a sneak preview of what's going on around the Institute. Scientists have shared some of the Institute's biggest discoveries at retreats over the years before they've appeared in journals. For example, In May 2013, former Tonegawa Lab members Steve Ramirez and Xiu Liu discussed their research on memory manipulation in mice two months before it made an international splash in *Science*.

In many ways, over many years, the Dana and Betty Fisher Retreat has been a uniquely valuable opportunity for The Picower Institute community.

Better Living Through Brain Chemistry



Studying neuromodulators such as serotonin and norepinephrine could help make them better targets for psychiatric or psychedelic drugs

A "wiring diagram" of the *C. elegans* worm shows neurons and muscle cells (dots) that express receptors for serotonin. Each color denotes a specific receptor. Some neurons express more than one. *Image courtesy Di Kang.*

Your brain is like a biological pharmacy. To regulate your internal states, such as arousal and mood, and your responses to the world, such as your sense of reward when you do something right or surprise when the results are unexpected, it dispenses doses of natural "drugs" called neuromodulators. Under healthy circumstances, these chemicals steer the activity of neurons to produce and sustain relatively long-lasting feelings and behaviors and then switches them to a different mode of activity when changing conditions warrant.

Trained by hundreds of millions of years of evolution, nervous systems do this with ease and precision. They synthesize and "prescribe" neuromodulators—serotonin, dopamine, endocannabinoids, norepinephrine, etc.—whenever and wherever they are needed, molecularly tweaking how neurons respond to the electrochemical signals they receive within the circuits they inhabit. In this way, neuromodulators can change the output of a circuit involved in a state or behavior.

With appreciation of the extraordinary influence of neuromodulators, humans have attempted to follow nature's example. We create or find drugs, such as Prozac, Ritalin, marijuana, psilocybin or MDMA, that manipulate neuromodulatory mechanisms in a quest to feel better.

But the imperfect efficacy of many pharmaceutical treatments and their significant risk of side effects lay bare a paradox: Like drugs, neuromodulators wash over millions of cells but they nevertheless achieve their broad-based effects quite precisely, finding the right receptors, on the right neurons at the right times in the right places even when multiple neuromodulators are all working in parallel in a somehow perfectly balanced soup. With incomplete knowledge of how the brain does this in health—and how it falters in disease—neuroscientists, drug designers, and psychiatrists haven't replicated the ability nature has evolved to affect neural circuits both broadly and precisely.

"We're increasingly appreciating the complexity and specificity of these neuromodulatory systems... A need for more targeted manipulations is going to be key."

-Brady Weissbourd

That is a main reason why improving fundamental understanding of how neuromodulation works is a priority among many researchers in The Picower Institute for Learning and Memory. Looking across different model organisms, different neuromodulators, and different behaviors and outcomes, they have published many recent studies shedding light on the mechanisms by which neuromodulators exert their effects. By adding to the knowledge of the field, they can help science catch up to nature, both in understanding how nervous systems work and how to better treat them. The field has made progress, of course, but much more is needed.

"We have a basic understanding of many modulatory systems, for example we know which neurons release serotonin and understand basic pharmacology of many serotonin receptors. But these neuromodulators can impact literally millions of neurons all at the same time," said Associate Professor and HHMI Investigator Steve Flavell. "There's not a strong understanding of the way that this parallel action on a million different units at once changes the way that animals are thinking, perceiving, feeling and acting. It's just really poorly understood."

Many psychiatric drugs, such as Prozac, seek to increase or decrease overall levels of neuromodulators, for instance by preventing cells from reabsorbing them. Sometimes this works, but in other cases it fails. The approach may be too coarse. More precise therapies, and ones with fewer side effects, will require figuring out the exact underlying mechanisms governing when neuromodulators are released, where they go, and how they affect their neural targets individually and *en masse*.

"We still don't understand how Prozac has such a specific effect in some cases and not in others, and we also don't understand why serotonin or norepinephrine reuptake inhibitors work," said Newton Professor Mriganka Sur. "It's lucky that we do get some efficacy. Based on function and the mechanism, people will one day build very specific molecules that affect very specific brain circuits."

Assistant Professor Brady Weissbourd agrees: "We're increasingly appreciating the complexity and specificity of these neuromodulatory systems and precisely when and where a modulator is released. The spatiotemporal dynamics of all that are super important. A need for more targeted manipulations is going to be key."

Examples of new findings about neuromodulatory mechanisms abound in Picower labs. This year in *Nature*, for instance, Picower Professor Li-Huei Tsai discovered that using light and sound to stimulate a particular brain rhythm in mice increases the release of the neuromodulatory neuropeptide VIP, which in turn compels astrocyte cells and the brain's vasculature to increase clearance of toxic waste proteins whose buildup is associated with Alzheimer's disease. Her lab is now investigating further roles that neuropeptides may have in the potential therapy.

For another example, in 2021 Associate Professor Gloria Choi found in *Nature* that the neuromodulator TRH was an essential component in switching neural circuit activity in male mice, such that when they smelled that females were sick, they'd forgo their typical mating instinct—a form of social distancing mediated by a neuromodulator. Moreover, Choi has published several other studies showing that immune system molecules called cytokines may have neuromodulatory properties, for instance by affecting social behavior when they act on cortical neurons. She has also seen initial evidence that cytokines might affect mood.

Serotonin system-wide

Flavell has been studying the simple *C. elegans* nematode to decipher a natural model of how serotonin works systemically across a whole animal. The transparent, microscopic worm has only 302 neurons (compared to tens of billions in a human) and has six different serotonin receptors (compared to 14 in people), but that simplicity is an asset, not a liability. The worm's neural circuits have been completely mapped out and all its genes can be manipulated. All its behaviors can be scrutinized and all its underlying neural activity can be measured. The tractability of *C. elegans* enabled Flavell's lab to perform what Weissbourd (who studied serotonin in mice as a graduate student) called a "dream" experiment: Flavell's team genetically knocked out every possible combination of the worm's six serotonin receptors so that he could see, brainwide, how that affected a particular serotonin-dependent food seeking behavior. Then the team also fluorescently tagged each receptor to map which neurons had which receptors. And finally, they watched the activity of each neuron amid instances of serotonin release to see how their combination of receptors related to their activity.

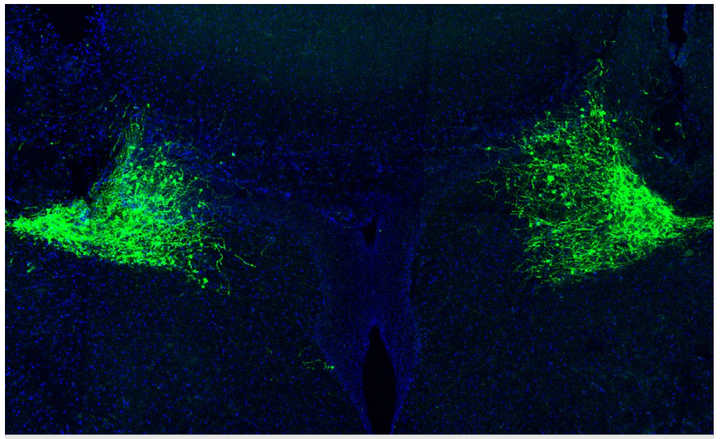
The study enabled Flavell to learn the distinct functions of each receptor, alone and in combination. The implications of the study for drug developers was clear: Given that many neurons may express different combinations of serotonin receptors, the effects of targeting one serotonin receptor or another could vary depending on how other receptors or the cell types that express them are functioning. In particular, the study highlighted how distinct serotonin receptors act in concert to change the activity states of neural circuits.

Flavell plans new experiments to build on these results. First he wants to drill down to see where each neuron expresses its various serotonin receptors and determine the logic of why they are where they are. To expose the "hidden variables" of where serotonin goes when it is released, how quickly it gets there and how long its stays, he plans to use optical labels of serotonin developed by Yulong Li at Peking University. And Flavell also hopes to work with the *C. elegans* model to tackle another problem that is very difficult to deal with in more complex organisms: how different neuromodulators work in combination.

"Individual cells have receptors for many of these neuromodulators and they're all acting together," Flavell said. "Any satisfactory understanding of how these systems work is inherently going to have to address the combinatorial nature of these neuromodulators."

Modulating memory

While Flavell is studying neuromodulators systematically across the worm, Sur and Assistant Professor Linlin Fan have each been investigating specific mechanisms in mice that demonstrate neuromodulators' relevance to learning and memory.



Green staining highlights the neural structure of the two locus coeruleus nuclei, one for each brain hemisphere, where norepinephrine is produced in the brain of a mouse. *Image by Gabi Drummond*

Earlier this year, Fan co-led a study in *Science* that identified a role for endocannabinoids in a process by which cells in the brain's hippocampus encode memories of specific locations. Using innovative optical techniques to stimulate and record electrical activity in the cells involved, Fan's team also used Li's optical neuromodulator labels to track the flow of endocannabinoids in living mice. The study provided suggestive evidence that when a "place cell" is being stimulated to remember a location, it uses a burst of endocannabinoids to quiet down inhibitory signals that would otherwise come from another neuron. To prove it, Fan plans new experiments in which she'll knock out the endocannabinoid receptors on the inhibitory cells and see what difference that makes to the electrical activity of the place cells. If the hypothesis is true, then the inhibitory neurons that lack endocannabinoid receptors, should persist in hindering the place cells' efforts to tune to the location they are learning.

(Continued on next page)

The significance of understanding how endocannabinoids help to implement learning and memory goes beyond the goal of understanding how the brain achieves a refined memory of where it's been. Endocannabinoid release increases amid epileptic seizures, so the study could shed light on how neural circuits might become perturbed when that happens. And because marijuana supplies the brain with external endocannabinoids, the research could help inform questions about how the drug might affect natural memory formation processes.

Sur's studies, meanwhile, have concerned how a different neuromodulator, norepinephrine, affects learning in different areas of the brain.

Traditionally dopamine has been associated with learning from reward and norepinephrine has been associated with arousal. But the two molecules are similar and even have the same chemical precursor, Sur said. Therefore Sur decided to investigate whether norepinephrine might have a role in learning from reward (and punishment), like its cousin dopamine.

This line of research in Sur's lab reached a major milestone in 2022 with a paper in *Nature* identifying specific mechanisms by which norepinephrine indeed influences learning. In the study the scientists rewarded mice with a refreshing sip of water if they pushed a lever when they heard a high-pitched tone, but gave them a little irritating puff of air if they pushed the lever when they heard a low-pitched tone. During the study the researchers varied each tone's loudness, thereby varying the certainty the mice had about whether they heard a tone and which one. Meanwhile, the researchers tracked and manipulated neural activity in the locus coeruleus, where norepinephrine is made, and monitored activity in other brain regions.

The study yielded several insights into how norepinephrine mattered to the task. One was that after the mouse pushed the lever (or didn't) in response to tone, norepinephrine reinforced the result. If the outcome was expected, there'd be just a small burst of the neuromodulator, but if the outcome was unexpected (for instance getting a puff of air instead of a reward), then there'd be a massive norepinephrine release in specific brain regions. After experiencing this signal of surprise mice would alter their behavior on the task, immediately factoring in what it learned from the surprising result.

The findings evoked another connection between norepinephrine and learning, Sur said. The neuromodulator is also associated with "single shot" learning, in which all that's required to indelibly remember an especially shocking stimulus is a single exposure. An unfortunate example is post-traumatic stress disorder.

"Norepinephrine marks surprising events," Sur said. "We know it's a marker of single shot events, good or bad and the bad ones need to be treated. We think that knowing the norepinephrine source, and the target that underlies this memory, would be a very focused target for treating such disorders."

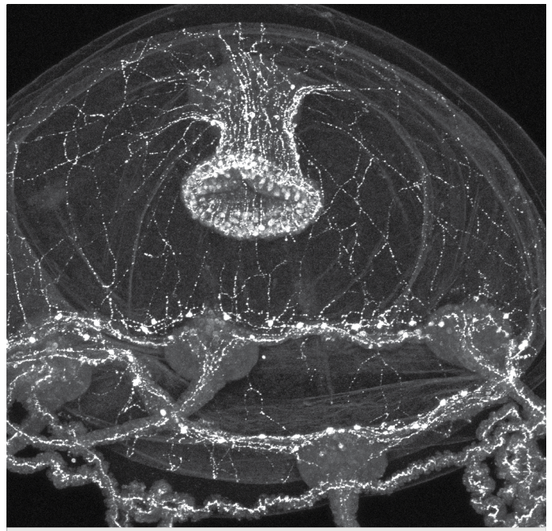
Evolving understanding

To Sur, one of the best testaments to the importance of neuromodulatory chemistry is its deep evolutionary roots.

"It exists in many of the humblest organisms, which leads us to ask: Why? What do they do?," Sur said. "They must have very profound functions."

One of those humble and evolutionarily distant organisms is Flavell's worms, which not only employ serotonin but also dopamine and other neuromodulators found in humans. An even more distant relative is the *Clytia hemisphaerica* jellyfish that Weissbourd studies. The branch of the evolutionary tree that the jellyfish descended along split off from the one humans emerged from right after the first nervous systems evolved.

"By comparing between jellyfish and other model organisms we can ask questions about what are the sort of deeply conserved principles of how our nervous systems work," he said.



Antibody staining highlights the RFamide neuropeptide in a C. hemisphaerica jellyfish. *Image courtesy Brady Weissbourd*

While jellyfish don't make serotonin or dopamine, Weissbourd has found that they employ about two dozen neuropeptides to send signals around their neural networks (even before there were neurons, *per se*, cells were using such peptides to communicate with one another). Weissbourd is systematically studying how each peptide affects the jellyfish's behaviors, both by knocking out the cells that make them, and seeing how behavior differs, and by synthesizing the peptides and seeing what happens when they are administered. If indeed at least some of the peptides are acting as neuromodulators—for instance by broadly yet precisely influencing circuit activity to represent and switch among internal states—then that would help confirm that even in this most distant of nervous systems, neuromodulation is still at work.

"I think there is a very ancient underpinning of how circuits can be modulated and flexible," Weissbourd speculated. "I think that dates back to the origins of nervous systems and may be conserved across all nervous systems."

This suggests that when we seek to manipulate our neuromodulatory systems with medicines or other drugs, we're tapping into a system that nature has been refining since before the dinosaurs. Only through research can scientists and clinicians hope to catch up.

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THE PICOWER INSTITUTE FOR LEARNING AND MEMORY

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September 24, 2024: Lectures

Michelle Monje, MD, PhD
HHMI, Stanford University

Erin Schuman, PhD
Max Planck Institute for Brain Research

September 25, 2024: Workshops

Hosted by The Picower Institute for Learning and Memory, MIT

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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, 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, Department of Brain and Cognitive Sciences; **Susumu Tonegawa**, Picower Professor of Biology and Neuroscience, Departments of Brain and Cognitive Sciences and Biology, HHMI Investigator, 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.