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'What were you thinking?'

How brain circuits integrate context to guide behavior
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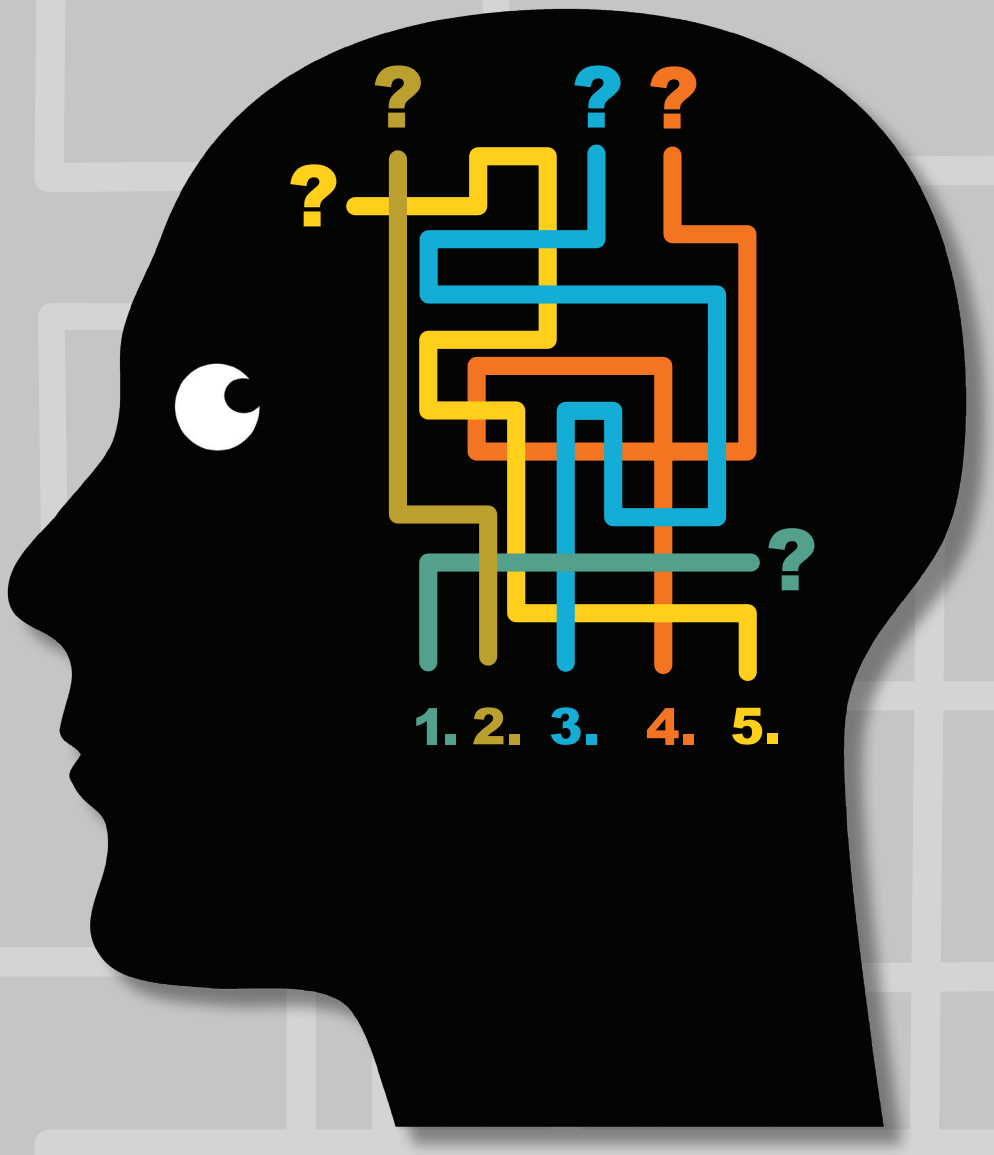
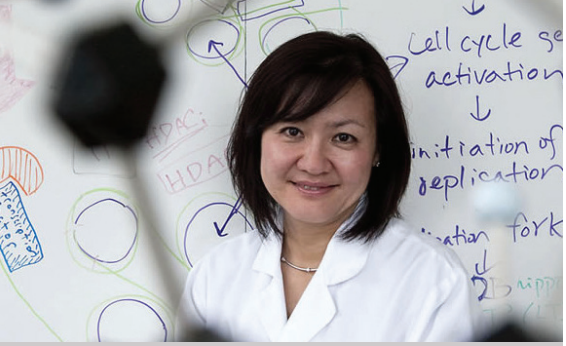


Neuroscience News

FALL 2021

THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY



DIRECTOR'S **MESSAGE**

Dear Friends,

In everyday experience (and good mental health), the connection between brain and behavior is simple and obvious. No one takes poetic metaphors like "go with your gut" or "follow your heart" literally. But when one seeks an explanation of *how* the brain produces our actions, a more scientifically apt metaphor is that it processes information via "circuits."

Indeed, because the computations that govern what we think, feel and do literally arise among connected series of electrically active neurons, neuroscientists embrace the circuit metaphor. In this issue we feature research from across the Institute delving into how brain circuits integrate information to produce behaviors. It's utterly fascinating to discover a new circuit and to show which regions and even which exact cells in an animal's brain make it do what it does. We describe several examples of that. But we also examine how the brain goes well beyond the simple circuit metaphor to ensure that our behavior doesn't just happen, but appropriately matches our complex, ever-changing contexts. We aren't light switches. We don't always want our circuits to do the same thing regardless of our circumstances. How does our circuitry flexibly incorporate context into its computations? See page 8.

While our cover story looks at circuits on a broad scale—sometimes reaching across the whole brain—next month our Fall Symposium will "zoom in" on where the neural circuit connections are made: the dendrites (see p. 11). Because we are still holding most events virtually (both because of the pandemic and to mitigate climate change), you can "Zoom" in and join us online.

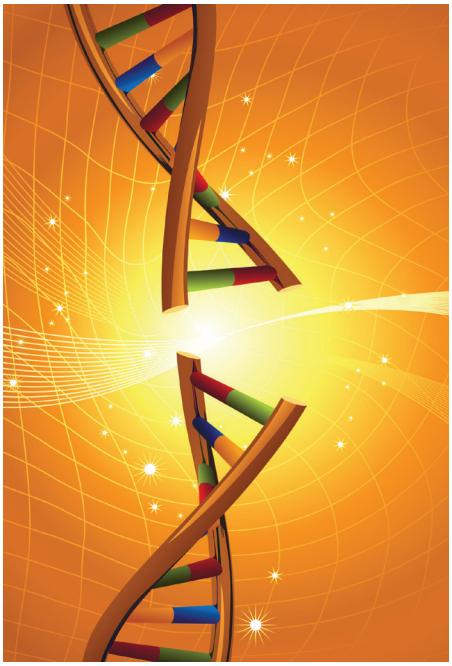
And on the following pages, you'll see all the latest news about our research and researchers, including work by undergraduate students from colleges across the country who've been visiting many of our labs the last few months as part of the MIT Summer Research Program (see p. 7).

Thanks for reading and connecting with us. We are glad you are part of our circuit.

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

Memory making involves extensive DNA breaking

To remember a dangerous experience, the brain makes a series of potentially dangerous moves: Neurons and other brain cells snap open their DNA in numerous locations—more than previously realized, according to a new study—to provide quick access to genetic instructions for the mechanisms of memory storage.



The extent of these DNA double-strand breaks (DSBs) in multiple key brain regions is surprising and concerning, said study senior author Li-Huei Tsai, Picower Professor of Neuroscience and Picower Institute director, because while the breaks are routinely repaired, that process may become more flawed and fragile with age. Tsai's lab has shown that lingering DSBs are associated with neurodegeneration and cognitive decline.

"We wanted to understand exactly how widespread and extensive this natural activity is in the brain upon memory formation because that can give us insight into how genomic instability could undermine brain health down the road," said Tsai, who is also a leader of MIT's Aging Brain Initiative. "Clearly memory formation is an urgent priority for healthy brain function but these new results showing that several types of brain cells break their DNA in so many places to quickly express genes is still striking."

In the new study in *PLOS ONE*, lead author and former graduate student Ryan Stott sought to investigate the full landscape of DSB activity in learning and memory. To do so, he and co-authors gave mice little electrical zaps to the feet when they entered a box to condition a fear memory of that context. They then assessed DSBs and gene expression in a variety of brain cell types shortly afterward. They also made measurements in mice who did not experience the foot shock to establish a baseline of activity for comparison.

The creation of a fear memory doubled the number of DSBs among neurons in the hippocampus and the prefrontal cortex brain regions, affecting more than 300 genes in each. Among 206 affected genes common to both, the researchers then looked at what those genes do. Many were associated with the function of the connections neurons make with each other, called synapses. This makes sense because learning arises when neurons change their connections (a phenomenon called "synaptic plasticity") and memories are formed when groups of neurons connect together into ensembles called engrams.

In a subsequent analysis of gene expression, the neuroscientists looked at not only neurons but also non-neuronal brain cells, or glia, and found that they also showed changes in expression of hundreds of genes after forming the fear memory. In glia, many of the DSBs following fear conditioning occurred at sites related to glutocortocoid receptors. Glutocortocoids are hormones secreted in response to stress. Further tests revealed that directly stimulating those receptors triggered the same DSBs as fear conditioning and blocking the receptors could prevent transcription of key genes for memory formation.

Tsai said finding that glia are so deeply involved in establishing memories from fear conditioning was an important surprise.

"This suggests that glia may have a much larger role to play in the response to stress and its impact on the brain during learning than previously appreciated," the researchers wrote.

Hippocampus needed to recognize image sequences but not single sights

A new MIT study of how a mammalian brain remembers what it sees shows that while individual images are stored in the visual cortex, the ability to recognize a sequence of sights critically depends on guidance from the hippocampus, a deeper structure strongly associated with memory but shrouded in mystery about exactly how.

By suggesting that the hippocampus isn't needed for basic storage of images so much as identifying the chronological relationship they may have, the new research published in *Current Biology* can bring neuroscientists closer to understanding how the brain coordinates long-term visual memory across key regions.

"This offers the opportunity to actually understand, in a very concrete way, how the hippocampus contributes to memory storage in the cortex," said senior author Mark Bear, Picower Professor of Neuroscience.

Essentially, the hippocampus acts to influence how images are stored in the cortex if they have a sequential relationship, said lead author Peter Finnie, a former postdoc in Bear's lab.

"The exciting part of this is that the visual cortex seems to be involved in encoding both very simple visual stimuli and also temporal sequences of them, and yet the hippocampus is selectively involved in how that sequence is stored," Finnie said.

To make their findings, the researchers trained mice with two forms of visual recognition memory discovered in Bear's lab. The first, called stimulus selective response plasticity (SRP) involves learning to recognize a non-rewarding, non-threatening single visual stimulus after it has been presented over and over. As learning occurs, visual cortex neurons produce an increasingly strong electrical response and the mouse ceases paying attention to the once novel, but increasingly uninteresting, image. The second form of memory, visual sequence plasticity, involves learning to recognize and predict a sequence of images. Here, too, the once novel but eventually familiar and innocuous sequence comes to evoke an elevated electrical response, and it is much greater than what is observed if the same stimuli are presented in reverse order or at a different speed.

In prior studies Bear's lab has shown that the images in each form of memory are stored in the visual cortex.

But the researchers were curious about whether and how the hippocampus might contribute to these forms of memory and cortical plasticity. To test that, they chemically removed large portions of the structure in a group of mice and looked for differences in the tell-tale electrical response each kind of recognition memory should evoke.

Mice with or without a hippocampus performed equally well in learning SRP (not only measured electrophysiologically but also behaviorally), suggesting that the hippocampus was not needed for that form of memory. It appears to arise and take hold entirely within the visual cortex.

Visual sequence plasticity, however, did not occur without an intact hippocampus, the researchers found. Mice without the structure showed no elevated electrical response to the sequences when tested, no ability to recognize them in reverse or when delayed and no inclination to "fill in the blank" when one was missing. It was as if the visual sequence —and even each image in the sequence—was not familiar.

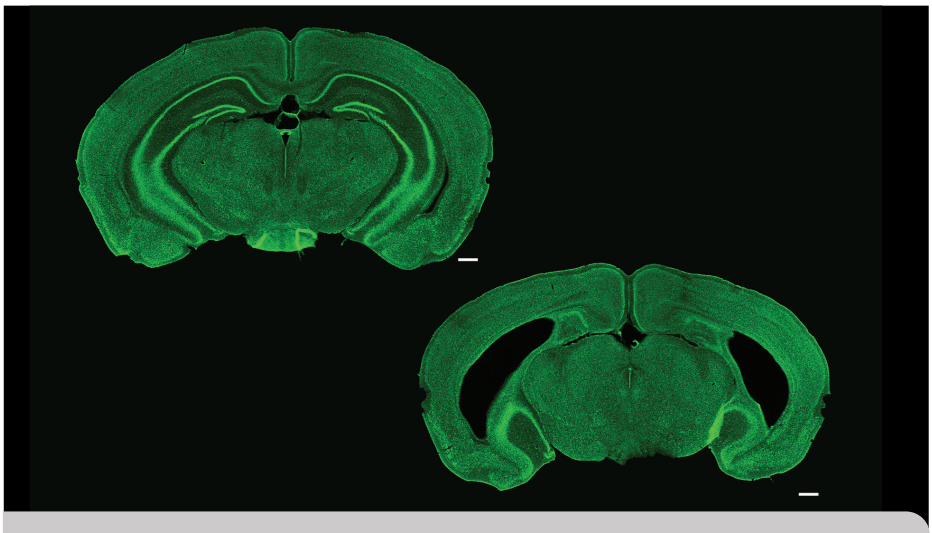
"Together these findings are consistent with a specific role for the hippocampus in predictive response generation during exposure to familiar temporal patterns of visual stimulation," the authors wrote.

The new study, Bear and Finnie said, produces a clear distinction for the division of labor in visual memory between simple recognition of images and the more complex task of recognizing sequence structure.

Previous research in the lab showed that SRP and visual sequence plasticity arise via different molecular mechanisms. SRP can be disrupted by blocking receptors for the neurotransmitter glutamate on involved neurons while sequence plasticity depends on receptors for acetylcholine.

The next question Bear wants to address, therefore, is whether an acetylcholine-producing circuit links the hippocampus to the visual cortex to accomplish sequence learning. Neurons that release acetylcholine in the cortex happen to be among the earliest disrupted in Alzheimer's disease.

If the circuit for sequence learning indeed runs through those neurons, Bear speculated, then assessing people for differences in SRP and sequence learning could become a way to diagnose early onset of dementia progression.



A pair of mouse brain cross-sections shows an unaltered one on the upper left and one with significant removal of the hippocampus on the lower right. ***Image credit: Peter Finnie.***

Different **rhythms**, cells take over as once-novel sights become familiar

To focus on what's new, we disregard what's not. A new study substantially advances understanding of how a mammalian brain enables this "visual recognition memory."

Dismissing the things in a scene that have proven to be unimportant is an essential function because it allows animals and people to quickly recognize the new things that need to be assessed, said Mark Bear, Picower Professor and senior author of the study in the *Journal of Neuroscience*.

"Everyone's appropriate behavioral response to an unexpected stimulus is to devote attentional resources to that," Bear said. "Maybe it means danger. Maybe it means food. It's absolutely essential for normal brain function that we're able to make a quick determination of whether a stimulus is novel or not."

People with schizophrenia and some autism spectrum disorders appear to struggle with this capability, Bear noted.

In 2006 Bear's lab discovered the first sign of visual recognition memory. Researchers detected a strong pattern of increasing electrical activity in the visual cortex as mice became familiar with an image on a screen. Subsequent research showed that this increase in electrophysiological response, dubbed SRP, or "stimulus selective response plasticity," correlated strongly with "habituation," or the behavioral loss of interest in exploring the increasingly familiar stimulus.

Since then, the lab has been working in mice to understand exactly how these phenomena emerge. Inhibitory neurons called parvalbumin (PV) expressing neurons appear to be crucial parts of the circuit. PV neurons are known to produce high frequency gamma rhythms in the cortex.

In the new study led by graduate students Dustin Hayden and Daniel Montgomery, Bear's lab shows that as novel visual patterns become familiar, the transition is marked by stark changes in the visual cortex. Gamma rhythms give way to lower frequency beta rhythms and the activity of PV neurons dies out in favor of a rise in activity by inhibitory somatostatin (SOM) expressing neurons.

The study, Bear said, therefore provides an externally measurable indicator of the transition from novel to familiar – the brain rhythm shift. It also offers a new hypothesis for how visual recognition memory is enforced: PV activity, which initially inhibits the SRP electrical response, eventually itself becomes inhibited by SOM activity.

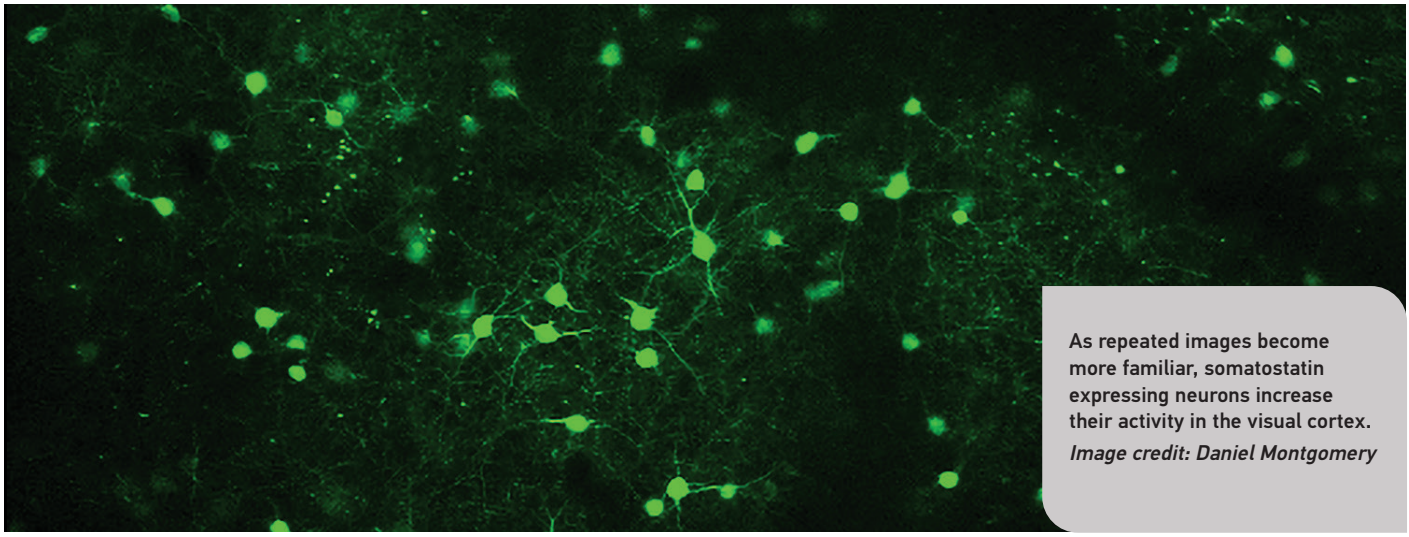
Bear's lab is working with Boston Children's Hospital researcher Chuck Nelson to determine if aberrations in SRP, such as this frequency transition, can be used as an early biomarker of autism spectrum disorders.

In the new study, the researchers showed mice the same simple image repeatedly over the course of several days. All the while they measured the SRP electrical response in the mice as well as neural rhythms. In parallel experiments, they engineered some mice so that their PV or SOM neurons would flash brightly when active. Then as mice watched the image, the scientists could watch for those flashes using a "two-photon" microscope.

On day one, when the image was novel, the spectrum of rhythms in the visual cortex was dominated by higher frequency gamma readings. As the days went on, gamma power diminished, replaced by a steady increase in low frequency beta power. To ensure this wasn't an unrelated transition, on day seven the scientists presented a new image and the familiar one. When the mice saw the new one, they again exhibited a gamma frequency dominated pattern. When they saw the same old original image, the visual cortex reproduced the pattern of increased beta power.

In a subsequent data analysis, the researchers found that the decline in gamma power and increase in beta power correlated significantly with the SRP growth of electrical activity, suggesting that they are indeed linked.

The two-photon microscope experiments revealed that PV neurons responded strongly to images when they were novel but that activity became replaced by increasing SOM activity over several days as the image became familiar.



As repeated images become more familiar, somatostatin expressing neurons increase their activity in the visual cortex.
Image credit: Daniel Montgomery

New research will test whether brain region is a key 'locus' of **learning**

Small and seemingly specialized, the brain's locus coeruleus (LC) region has been stereotyped for its outsized export of the arousal-stimulating neuromodulator norepinephrine. In a new paper and with a new grant from the National Institutes of Health, a Picower Institute lab is making the case that the LC is not just an alarm button but has a sophisticated impact on learning, behavior and mental health.

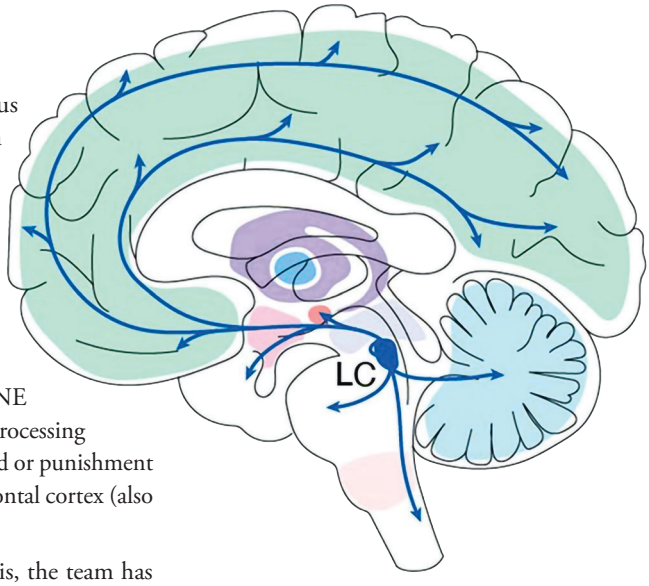
With inputs from more than 100 other brain regions and fine control of where and when it sends out norepinephrine (NE), the LC's tiny population of surprisingly diverse cells may help regulate learning from reward and punishment, and then applying that experience to optimize behavior, said Mriganka Sur, Newton Professor of Neuroscience.

"What was formerly considered a homogenous nucleus exerting global, uniform influence over its many diverse target regions, is now suggested to be a heterogeneous population of NE-releasing cells, potentially exhibiting both spatial and temporal modularity that govern its functions," wrote Sur, postdoc Vincent Breton-Provencher and graduate student Gabrielle Drummond in a review article in *Frontiers in Neural Circuits*.

The article presents copious emerging evidence from Sur's group and many others, suggesting that that the LC may integrate sensory inputs and internal cognitive states from across the brain to precisely exert its NE-mediated influence. It affects actions by throttling NE to the motor cortex and the processing of resulting feedback of reward or punishment by throttling NE to the prefrontal cortex (also see p. 9).

To investigate that hypothesis, the team has begun working with a $2.1 million, 5-year NIH grant awarded in April.

Understanding the true nature of how the LC works could be useful for improving treatments for certain disorders, Sur said. A potential treatment for PTSD, for instance, involves damping receptiveness to NE, but that also promotes drowsiness. A more principled and precise treatment could improve efficacy and reduce side effects, he said.



A diagram shows the location of the locus coeruleus (LC) and its main circuit projections.

Moreover the LC is an early region affected in Alzheimer's disease, he said. Addressing that loss in the right way could help sustain forms of learning and cognition.

When growing 'minibrains,' hindering enzyme has surprising effects on growth

Like many around the world, the Picower Institute lab of Newton Professor Mriganka Sur has embraced the young technology of cerebral organoids, or "minibrains," for studying human brain development in health and disease. By making a surprising new finding about a common practice in the process of growing the complex tissue cultures, the lab has produced both new guidance that can make the technology better, and also new insight into the important roles a prevalent enzyme has in natural brain development.

To make organoids, scientists take skin cells from a donor, induce them to become stem cells and then culture those in a bioreactor, guiding their development with the addition of growth factors and other chemicals. Over the course of weeks, the stem cells become progenitor cells that multiply and then go on to become, or "differentiate" into, neurons or other brain cell types.

As the cells grow and develop together, they simulate many of the basic processes that occur when real brains take shape. When cell donors have genes that cause disease, the organoids grown from their cells reproduce underlying disease characteristics. The Sur lab uses organoids to study Rett Syndrome, a devastating autism-like condition with a genetic underpinning.

Labs growing organoids often improve the viability of the cells by adding a small molecule chemical called CHIR 99021 to inhibit the activity of a ubiquitous natural enzyme called GSK3-beta. In the new study in *PLOS ONE* Picower Fellow Chloé Delépine and co-authors confirmed that while different doses of CHIR 99021 indeed keep cells alive, they have opposite effects on organoid growth – low doses promote growth but high doses constrain it and very high doses will stop it altogether. That information alone has obvious implications for labs using varying doses of CHIR 99021.

In natural brains, the study suggests, GSK3-beta likely plays a key role in the proliferation of progenitor cells, their differentiation into mature brain cells, and the propensity of those cells to migrate.

Bear earns amblyopia research award

Research to Prevent Blindness (RPB) has granted Picower Professor Mark F. Bear the RPB Walt and Lilly Disney Award for Amblyopia Research to support his work on a potential treatment for the disorder, the most common cause of lost vision starting in childhood, affecting millions around the world.

Amblyopia emerges early in development when vision in one eye is impaired, for instance by a cataract or other impediment. Traditional therapy for amblyopia involves correcting the impediment and then covering the "good" eye with a patch to promote use of the formerly compromised eye. This treatment can help, but often only restores vision partially and becomes ineffective after about age 8.

In decades of investigating the development of visual cortex, Bear's lab has discovered fundamental mechanisms of how amblyopia emerges in the brain, leading to a new potential therapy. They showed that when an eye is deprived of normal vision, the connections from that eye to visual cortex undergo a process called "long-term depression" (LTD). But Bear's lab has also discovered that these connections can be rejuvenated when inputs are temporarily silenced entirely. In collaboration with researchers at Dalhousie University, his lab has shown in multiple animal models that "rebooting" a formerly deprived eye can occur after brief treatment of the retinas with a local anesthetic. This procedure restores vision much more fully than patch therapy, even at an adult age.

The new award will help the lab continue testing this approach for translation to clinical use in people, said Bear, an investigator in The Picower Institute.

"I am honored to receive this prestigious award, which will accelerate progress toward translating our discoveries in animals to develop new treatments for amblyopia based on the fundamental principles of synaptic plasticity I have spent my life working to elucidate," Bear said.

Postdocs earn interdisciplinary Schmidt Science Fellowships

Two postdoctoral researchers in Picower Institute labs are among 28 around the world to have been named to a competitive Schmidt Science Fellowship, an award created in 2017 to advance interdisciplinary studies among early career researchers.

"An initiative of Schmidt Futures, delivered in partnership with the Rhodes Trust, the Schmidt Science Fellows program brings together the brightest minds who have completed a PhD in the natural sciences, mathematics, engineering, or computing, and places them in a postdoctoral fellowship in a field different from their existing expertise," according to the announcement of the awards by benefactors Eric and Wendy Schmidt.

In all, four Schmidt fellows are connected with MIT, including two in the mechanical engineering and civil and environmental engineering departments.

SIRMA ORGUC, a newly named fellow in the lab of Picower Institute investigator and Edward Hood Taplin Professor Emery N. Brown, earned her PhD this year at MIT in the Electrical Engineering and Computer Science Department. Her doctoral studies blended electronics, materials science and algorithm development in research on wearable and implantable interface technologies for biomedical and neuroscience applications. During her postdoc in the Brown lab through MIT's Institute for Medical Engineering and Science, Orguc will "shift gears" to learning about computational neuroscience, machine learning, neurophysiology and control theory with the aim of building closed-loop neuroscience systems.

"Controlling the level of unconsciousness under general anesthesia, real-time prevention of epileptic seizures, and working towards treating disorders such as chronic depression are example applications of interest," Orguc said. "The Schmidt Science Fellows community believes in the power of interdisciplinary science to drive innovation and discovery and make a positive impact in the world. I am beyond grateful and excited to be part of such a community. The fellowship gives incredible flexibility to researchers and I will try to make the most of it."

REBECCA PINALS earned her PhD this spring in UC Berkeley's Chemical and Biomolecular Engineering Department after studying fundamentals of how engineered nanomaterials interact with biological environments. To build on her insights into designing nanosensors for biomedical applications, she then joined the lab of Picower Professor and Picower Institute Director Li-Huei Tsai. There, Pinals will investigate the mechanistic underpinnings of Alzheimer's disease by developing nanosensors for key disease biomarkers and applying them to probe the disease in human brain tissue models.

"Implementing the tools of nanotechnology to study Alzheimer's will deepen our understanding of the underlying disease drivers by providing the requisite spatial, temporal, and chemical resolution information on biomarkers during disease onset and progression," she said. "I am beyond excited for this opportunity to pursue impactful research at the Picower Institute in an orthogonal field to my own background, and to be a part of the Schmidt Science Fellows community."

Summer students thrive in Picower labs

A college student could imagine many ways to spend a summer, but for 11 undergraduates at universities from the Caribbean to California, an uncommon passion for science and an eagerness for immersion in current, world-class research made joining Picower Institute labs a compelling choice.

At a bustling poster session in early August where they presented their work, it was clear that the students hailing from underrepresented or disadvantaged backgrounds and non-research intensive home institutions made the most of their participation in the MIT Summer Research Program (MSRP) in Biology and Brain and Cognitive Neuroscience. They said the experience, skills, contacts, and inspiration they gained can advance their academic ambitions.

Performing experiments to study possible treatments for the developmental vision disorder amblyopia in the lab of Picower Professor Mark Bear gave Alysa Alejandro-Soto, a student at the University of Puerto Rico Mayaguez, an inspiring exposure to fundamental lab neuroscience that can also have direct, future relevance to patients, she said.

"I really wanted to do neuroscience research but I hadn't been able to do it in my undergraduate studies," she said of her work alongside postdoctoral mentor Hector de Jesús-Cortés. "I want to do an MD/PhD and it's really exciting for me to see how this could be applied clinically."

Hanoka Belai said that her summer in the lab of Latham Family Associate Professor Myriam Heiman has recharged her interest in pursuing a neuroscience degree. A biotechnology major at Roxbury Community College, Belai said her research with postdoctoral mentor Brent Fitzwalter to advance a novel strategy for treating the terminal neurodegenerative condition Huntington's disease was exciting because she wants to learn science to help people.

Heiman said she was delighted to host two MSRP students this summer. Along with Belai, she and graduate student Preston Ge also welcomed Rim Bozo who is on her way to Dartmouth College after graduating from Pioneer Charter School Of Science near Boston. Bozo said the chance to go from high school labs to working on studies of Parkinson's disease at MIT provided exceptional preparation for college.

"They are both outstanding young scientists," Heiman said. "The MSRP students are always very motivated and eager to learn so we always look forward to working with them."

In all, eight Picower labs hosted at least one MSRP student.

Paola Alicea-Román from the University of Puerto Rico Humacao first worked with the Bear lab last summer, but could only do so virtually because of the Covid-19 pandemic. Even though her research applying a deep learning algorithm to assess the vision of mice with amblyopia was computational, she said, she reveled in the chance to be in the lab in person this year. Being there allowed her to help shape the experiments providing the data, and gave her opportunities to network with professors, fellow women in science and graduate students.

Professor Elly Nedivi visits with MSRP student Miriam Goras at her poster.

Relationships and mentorship are an especially important component of MSRP for many students who participate. Sonia Okekenwa, a student at Fisk University in Nashville, said a particularly valuable aspect of her work in the lab of Picower Professor Li-Huei Tsai was the frequent dialogue she had with postdoctoral mentor Vishnu Dileep and other lab members, who challenged her to think deeply about what she was finding out in her research mapping where DNA breaks open to enable neuronal processes (see p. 2).

Miriam Goras of Arizona State, who worked in the lab of William R. and Linda R. Young Professor Elly Nedivi with postdoc Baovi Vo, said she similarly valued the challenge of having to figure out genuine problems with no pre-determined answers. For instance, during her work this summer studying the molecular biology of treatment for bipolar disorder, she had to dig into the scientific literature to troubleshoot biochemical methods in the optimization of her cell culture experiment.

Several other Picower MSRP students, who included Jordina Pierre of the University of the Virgin Islands, Miguel Coste of Notre Dame, Joshua Powers of George Washington University, Patricia Pujols of Bayamon Central University, and Hannah Caris of Pomona College said they also valued the exposure, training, and guidance they gained through MSRP, which is coordinated by Director of Diversity and Science Outreach Mandana Sassanfar.

Powers, in fact, was back for his fourth summer after first engaging with MIT programs as a high schooler. His experience in the Flavell lab with postdoc Cassi Estrem has helped him clarify that he wants to pursue research as a career.

"The Flavell lab continues to show support for me, to teach me and go out of their way to make sure I'm keeping up with them for my benefit," he said.

For Powers and his colleagues, these have been summers well spent.

‘What were you thinking?’

How brain circuits integrate many sources of context to flexibly guide behavior

Mating is instinctual for a mouse but sometimes, for instance when his potential partner smells sick, a male mouse will keep away. When Mark Hyman Jr. Career Development Associate Professor Gloria Choi and colleagues published a study in *Nature* in April revealing how this primal form of social distancing occurs, they provided an exquisite (and timely) example of how brain circuits factor context into behaviors, making them adaptive and appropriate even when they are innate, or “hardwired.”

When the odor of illness enters the mouse’s nose, that stimulates neurons in its vomeronasal organ to send an electrical signal through a nerve to the brain’s olfactory bulb. Cells there, Choi’s team discovered, relay the signal on to neurons in a region called the cortical amygdala that govern the mating instinct. Finally, completing the health-preserving circuit that will inhibit the mating instinct, those neurons pass on the message to brethren in the neighboring medial amygdalar nucleus. In so doing, this sequence feeds a sensory context, the female’s ill odor, into a circuit to override the default context of an internal state, the instinct to mate. The researchers even showed that by artificially stimulating cortical amygdala neurons they could prevent a mouse from mating with a healthy partner and by artificially silencing those same cells they could make a mouse mate with an ill-smelling one.

As you can learn below, the brain has much greater flexibility in how it operates than the electrical circuits that power your house or even the chips that drive your cell phone. But fundamentally it is the routing of electrical signals from neuron to neuron that forms the basis not only for how we behave, but also how we match behavior appropriately to the circumstances we encounter, Choi said.

“The closest component to behaviors and internal states, and changes in those, are still believed to be neurons and circuits,” she said.

Understanding how brain circuits produce behavior is an exciting area of neuroscience research, including in many Picower Institute labs. Their studies are helping to elucidate how the brain’s anatomy is arranged to process information, and how the many dimensions of flexibility that the central nervous system overlays upon that infrastructure can integrate context to guide appropriate behavior. Context, after all, comes from many sources in many forms—from the senses, like scents and sounds and sights; from internal states, like mating drive or hunger or sleepiness; and even from time and place and from what we’ve learned and remember.

So what were you thinking when you did “this” instead of “that”? You were thinking about the context and relying on your brain’s ability to account for it.

Chemical control

The popular “circuit” metaphor makes it easy to think of neurons as merely switches and wires that pass electrical transmissions from one point to another. And indeed they do that, although instead of being screwed and soldered to metal contacts, they use molecules called neurotransmitters to send signals across tiny junctions called synapses. But if that were all that was going on, the brain would be pretty static and it is anything but. Many members of the Institute’s faculty study how learning occurs and memories are formed when the brain changes its synapses to create or edit circuit connections, but none of that is strictly necessary for existing circuits to flexibly control behaviors that we’ve already learned or that are innate. The brain has other ways to flexibly change how it operates. Choi’s team, for instance, found that the behavioral change of inhibiting mating could not occur without the cortical amygdala neurons also sending a chemical, thyrotrophin releasing hormone (TRH), to the medial amygdalar nucleus neurons.

In the lab of Lister Brothers Associate Professor Steven Flavell, researchers study how internal states and behaviors emerge and change using a worm so simple that its complete, invariant “wiring diagram” has been completely mapped out for decades. Yet even in *C. elegans*, with its exact total of 302 neurons, scientists are still discovering how the animal adapts its actions to survive and thrive in a world of ever-changing contexts.

“Since 1986, that wiring diagram has been staring at researchers,” Flavell quipped. “Many of the small circuits embedded in the

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wiring diagram have been closely studied, while others haven't. But a key question that we are trying to answer is how does the whole system work. How are these circuits coupled together to give rise to so-called 'brain states'?"

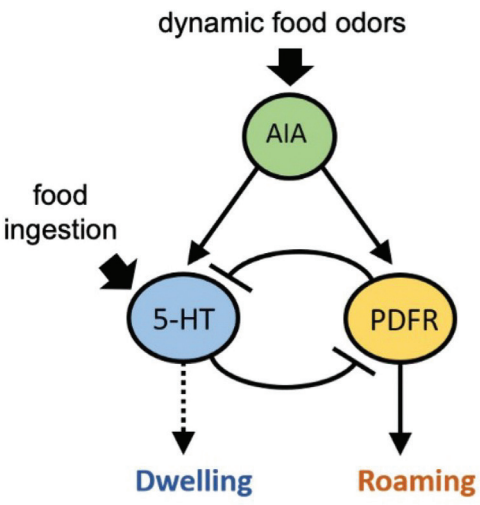
In several studies Flavell has shown how a small number of neurons encode contexts and then signal that those circumstances are afoot by releasing chemicals called "neuromodulators" to many other neurons, giving rise to a brain state. Just as TRH may be doing in the circuit Choi uncovered, neuromodulators such as serotonin and dopamine, which are also ubiquitous in humans, add an extra dimension of tuning that can change, or "modulate," how hardwired circuits process information and output behaviors, Flavell said. Neuromodulators can make neurons more or less electrically excitable given the same degree of input, Flavell explained. They can also make transmission at individual synapses more or less effective.

"The physical connections are like a roadmap, but the way that traffic is actually flowing on the road, the way that neurons are coupled to each other, is dynamic and changes with the animal's context," Flavell said. Neuromodulators are one way to make that happen.

For instance, in a 2019 paper in *Cell*, Flavell's lab showed how a hungry worm knows to slow down and savor a patch of yummy bacteria when it finds one. A single neuron called NSM extends a little tendril called a neurite into the worm's pharynx. Equipped with bacterial sensors (that turn out to also be present in the human intestine), the neurite detects when the worm has started to ingest and mash up its food. NSM releases serotonin, which finds its way to many of the neurons in worm's brain that control locomotion. Upon sensing the serotonin, they hit the brakes.

In a more recent study in *bioRxiv*, the lab takes their investigation of neuromodulators even further. The study characterizes exactly how serotonin release from NSM modulates that activity of specific neurons in the C. elegans brain. In addition, Flavell's group found that a neuron called AIA integrates information from sensory neurons about the smell of food. NSM can help determine what it does with that information, depending on whether it detects that the worm is eating or not. If it is, the smell of food (detected by AIA) reinforces that it should stick around to continue dining, a state maintained with serotonin. If the worm isn't eating, the food smells signal that the animal should go exploring to find the source of that enticing odor. AIA, in that case, can instead trigger neurons that produce a different neuromodulator, called PDF, that cause the worm to start roaming (toward the food odor). Even in the simple circuitry of *C. elegans*, context changes how neurons interact, giving the animal flexibility to process sensory information.

That neurons capable of emitting neuromodulators can exert far-flung influence over behavior is illustrated by research in Newton Professor Mriganka Sur's lab, too. There Sur's team has a focus on a deeply situated, tiny brain region called the locus coeruleus (LC) that happens to supply most of the brain's norepinephrine (also see p. 5). Classically, neuroscientists have regarded norepinephrine from the LC as increasing the brain's internal state of general arousal, but recent research in the Sur lab suggests it has profound, context-dependent effects on learning and behavior.



In the C. elegans worm, when the AIA neuron detects a food smell, if the worm is eating a circuit will make it linger. If it is not eating, a different circuit will compel it to roam to find the source of the smell.

For instance, members of the lab have trained mice to expect a reward if they push a lever after hearing a high-pitched tone; the mice also receive an unexpected and irritating puff of air if they mistakenly press the lever after a low-pitched tone. By varying the loudness of the tones, the researchers can also vary the certainty the mice have about what tone they heard. Sur's lab has found that the louder a high-pitched tone, the more norepinephrine a mouse will send to the motor cortex, which plans movement, before pushing the lever – as if greater certainty prompts it more strongly to push the lever.

Once the lever has been pushed and the mouse gets its feedback of reward or air puff, LC neurons producing norepinephrine then act to fine-tune learning by calling attention to any surprising feedback, Sur's team has seen. For instance, if the tone was high pitched and faint, but the mouse took the risk to push the lever, the neurons will send a burst of norepinephrine to the prefrontal cortex to note that pleasant surprise. The biggest post-push surge of the neuromodulator, however, occurs when the mouse guesses wrong: that norepinephrine release to the prefrontal cortex appears to signal that the adverse result must be noted. Sure enough, Sur said, the team has seen that the mouse's performance typically improves after making an error. The LC's neuromodulatory actions may contribute to that behavioral improvement, though more research is needed to prove it.

Sur's is not the only research in The Picower Institute showing that the LC communicates with the prefrontal cortex to improve task performance, though. Last November in the *Proceedings of the National Academy of Sciences*, Picower Professor Susumu Tonegawa's lab showed that LC norepinephrine neurons connect via distinct circuits to two different parts of the prefrontal cortex to endow mice with both the ability to curb impulses (i.e. to not "jump the gun" when waiting to perform tasks) and to ignore distractions, such as false cues.

Rhythms among regions

Much as the Sur and Tonegawa labs have been investigating the LC, Fairchild Professor Matt Wilson's lab studies how a different region appears to be a key hub for integrating contexts such as location, motion and memories of reward into behaviors such as navigation: the lateral septum (LS). As

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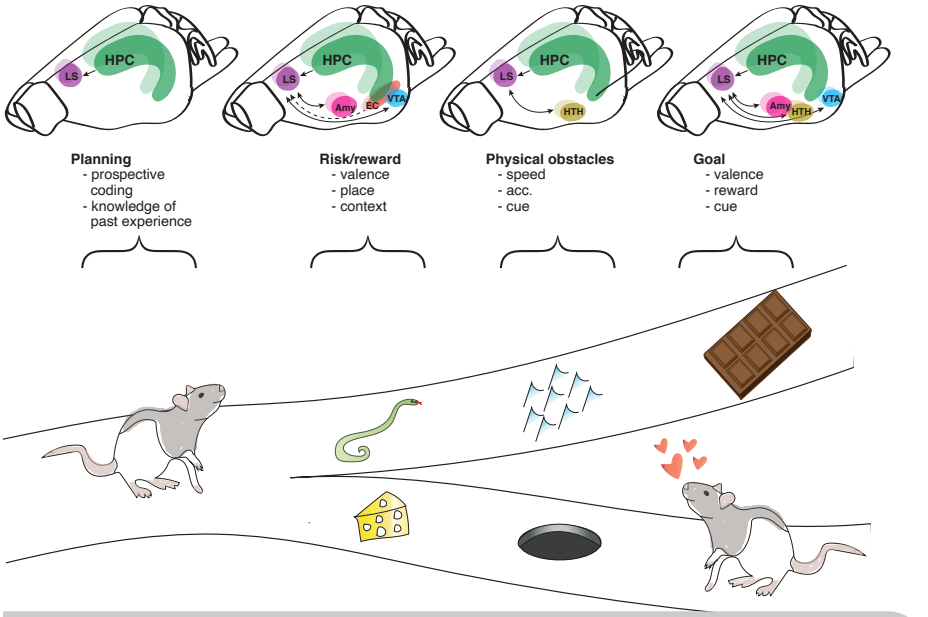
rats learn to find and return to the location of a reward in a maze, the lab's extensive measurements of electrical activity among neurons in the LS shows that those cells are taking in and processing crucial contextual input from many other regions. The LS then appears to package that context to help direct the rat's navigational plans and actions.

Over the past two years, Wilson and former graduate student Hannah Wirtshafter have published papers in *Current Biology* and in *eLife* showing that populations of LS neurons distinctively encode place information coming from the hippocampus, reward information coming from the ventral tegmental area and speed and acceleration information coming from the brainstem. The encoding is apparent in changes in the timing and rate at which the neurons "fire," or electrically activate, in these different contexts. Some LS neurons, for example, become especially active specifically when the rat nears the reward location. In a new article published in *Neuroscience and Biobehavioral Reviews* in July, Wilson and Wirtshafter combined their observations with those of other labs to propose that the lateral septum packages all this contextual information into an "integrated movement value signal."

"The lateral septum has a ton of different inputs," Wirtshafter said. "What could the animal be doing with place-related firing that's reward modulated and then velocity and acceleration? The answer, we think, based on where the LS outputs to, is that it is sending a signal about the context and whatever reward is part of that context. It includes what movement needs to be done and whether that movement is worth it in that context."

While there are ample signs in the research that neuromodulators such as dopamine help the LS communicate about contexts like the feeling of reward, the studies also highlight the key role of another mechanism of flexibility: brain rhythms. Also known as brain waves or oscillations, these rhythms arise from the coordinated fluctuation of electrical activity among neurons that are working in concert. They allow neurons in brain regions to broadcast information and neurons in other regions to tune into those broadcasts, so that they can work together to perform a function, Wilson said.

"These brain dynamics ensure that whoever is sending the information and whoever is receiving the information are doing it at the same time," Wilson said.



Along its way, a rat might encounter many different contexts. Researchers speculate that different brain circuits (top) involving the lateral septum (LS) help integrate that context to guide appropriate behavior. Other key regions are the hippocampus (HPC), amygdala (amy), hypothalamus (HTH), entorhinal cortex (EC) and ventral tegmental area (VTA). *Illustration by Hannah Wirtshafter.*

In fact, Picower Professor Earl Miller, who has published numerous studies on how brain rhythms guide the flow of information across the many regions of the brain's cortex, uses much the same kind of traffic analogy in talking about the function of rhythms that Flavell uses when talking about neuromodulators. Much as those chemicals can, oscillations also flexibly direct the flow of information on the network of "roads" that physical circuit connections create. The traffic metaphor perhaps combines well with the broadcasting one: Just like drivers who tune into a radio traffic report can decide to take an alternate route when they hear about an accident ahead, neurons in a brain region may act differently when they tune into new contextual information coming in from another brain region.

Wilson and Wirtshafter's research, for example, demonstrates that lateral septum neurons tune into the hippocampus's broadcast of location information via a specific "theta" frequency of brain waves. In particular, movement through a place is represented by the phase (peak or trough) of the theta waves with which neurons spike.

"In the hippocampus, the phase at which a cell fires during theta can communicate information about the current, prospective, or retrospective spatial location," Wilson and Wirtshafter wrote in their article. "For instance, …firing of individual hippocampus place cells begins on a particular phase of theta rhythm and progressively shifts forward as the animal moves through the place field."

So maybe you are not a mouse deciding whether to mate or a rat rooting through a maze for a treat, but you are a person who has stayed out late at a friend's house. Your internal state is that you are tired. You could head out on long drive home to the reward of your clean, warm bed, or you could sleep on your friend's notably mustier couch and explain it your spouse the next morning. Then you remember from the drive to your friend's place earlier, that there was an all-night rest stop along the highway where you could get coffee. Whether you decide to take the wheel or your friend's offer of the couch will come from how a combination of neuromodulators and rhythms route information along circuits through key brain regions to integrate all this context—your internal state of tiredness, the memory of where that rest stop was, and the reward of your bed (or the punishment of an angry spouse who might ask "What were you thinking?"). Your brain gives you all the flexibility you need.

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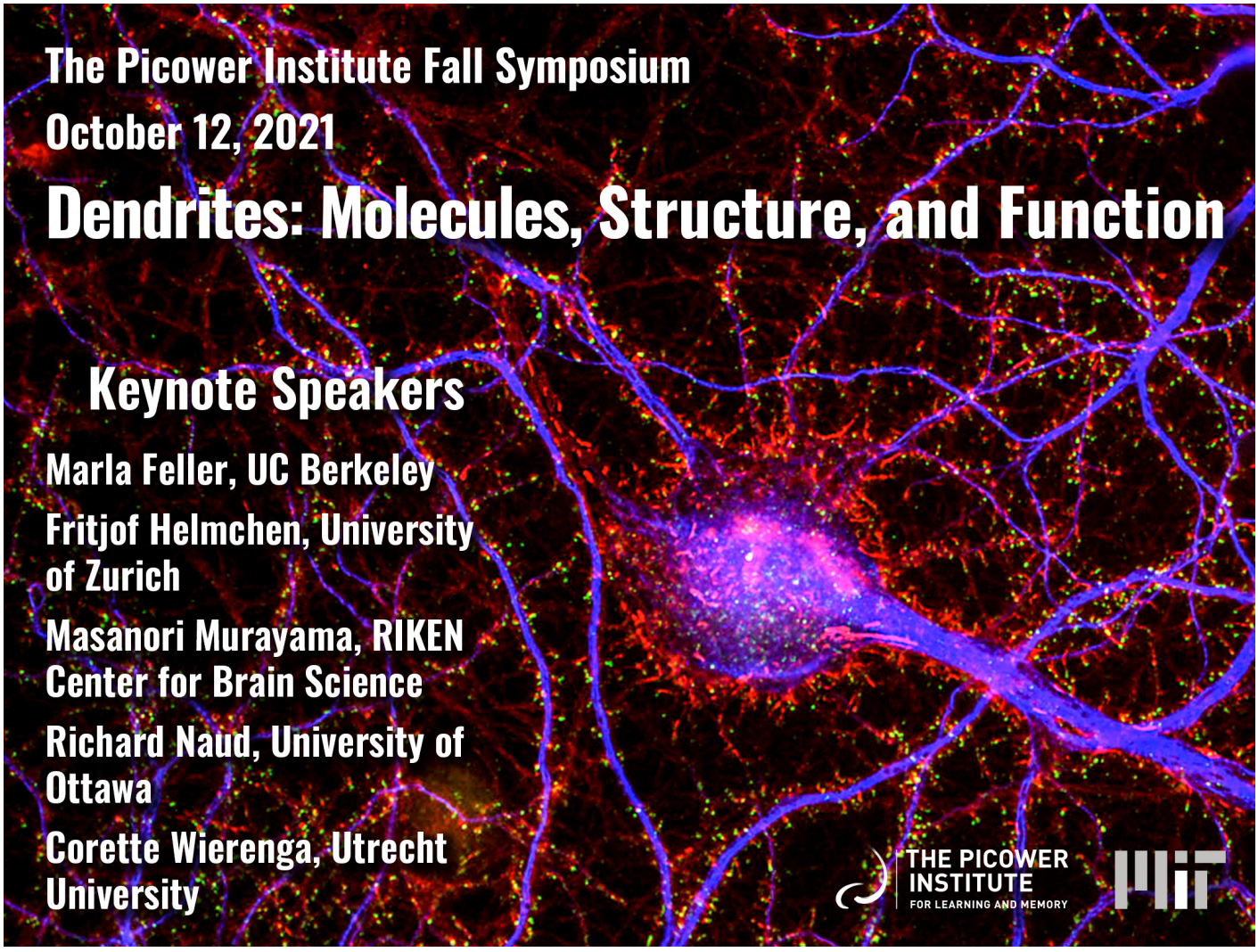

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Choi photo by Justin Knight