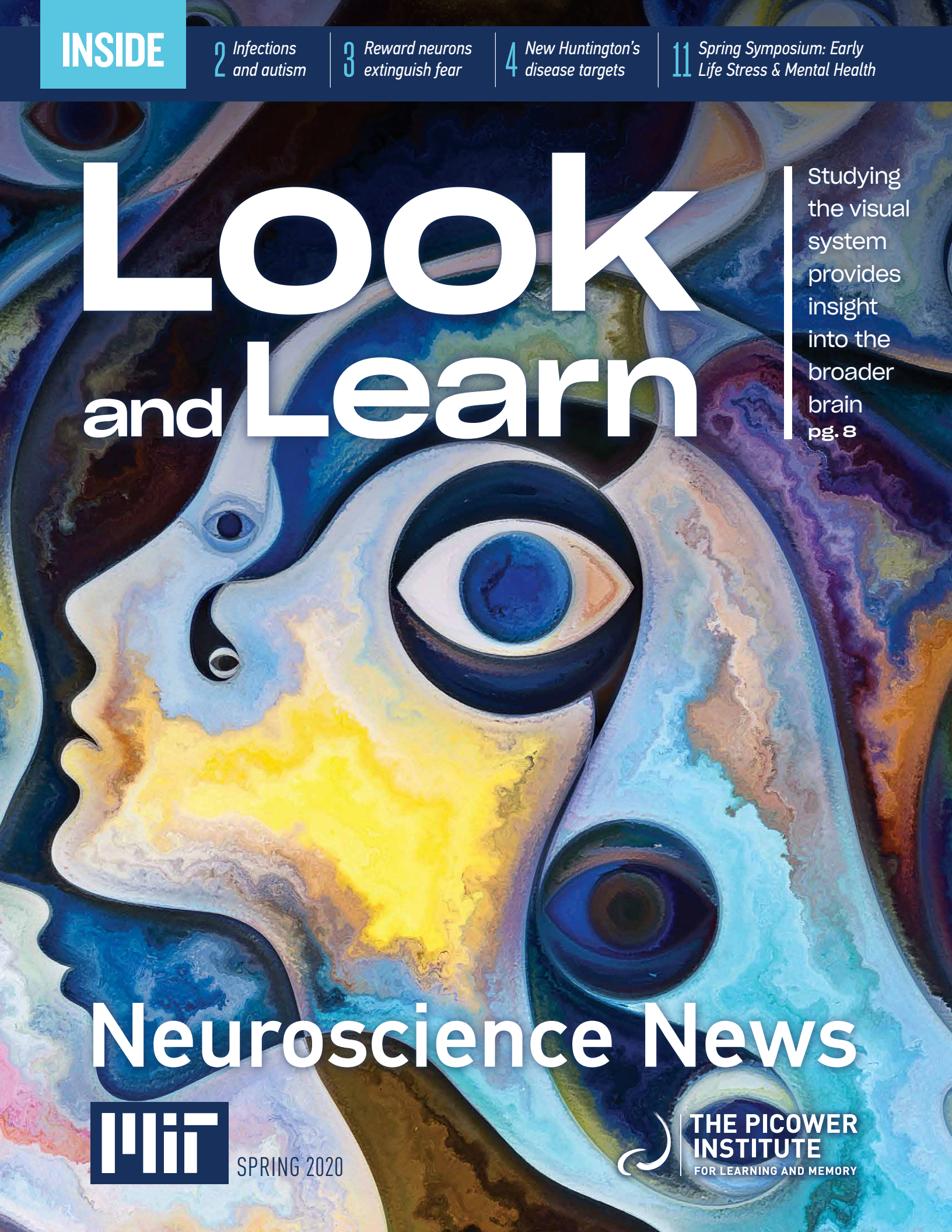


Look and Learn

Studying the visual system provides insight into the broader brain
pg. 8

Neuroscience News

SPRING 2020

THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY

DIRECTOR'S **MESSAGE**

Dear Friends,

To learn and remember anything, or to interact with or consider the world, the brain must acquire experience via the senses. Scientists eager to observe the brain's mechanisms and processes for storing and employing information therefore understand that the primary visual cortex – where the brain analyzes what the eyes see – is a powerful place to look. In neuroscience at large, and certainly here at the Picower Institute, some of the most exciting discoveries about the broader brain have come from research involving the central visual system.

In this edition's cover story (p. 8) we focus on how four Picower labs use the visual system to study the brain at scales ranging from individual synaptic connections between pairs of neurons all the way up to complex cognition and behavior. These studies have not only helped us contribute to fundamental scientific progress, but also have generated new methods and strategies for addressing neurological and psychiatric diseases.

One does not have to be a neuroscientist to know that among our five senses, vision is especially exalted. Consider how we use visual metaphors to describe our thinking. To say we understand, we often say, "I see." When we recognize that an understanding has advanced our knowledge we call it an "insight." Our expectations for the future are our "outlook." And to praise someone's ideas, we might call them a "visionary."

Indeed this issue reports on a variety of Picower Institute "insights," such as studies that explain the mysterious connection between fever and temporary relief of autism symptoms (p. 2) or the uncanny similarity between reward and overcoming fear (p. 3).

We also acknowledge the vision of Jean-Jacques Degroof, who was an early partner in my lab's efforts to test a potential Alzheimer's therapy (p. 7) and the JPB Foundation of Barbara Picower, with whom we'll present our biennial Spring Symposium, "Early Life Stress and Mental Health" (p. 11). Held and livestreamed May 14, the event is dedicated to combatting adverse childhood experiences and improving the lifelong outlook of our youth.

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

Immune molecule reduces autism symptoms in mouse study

As two large studies and many parental reports document, some autistic children's behavioral symptoms diminish when they have a fever. It has been unclear why, but a new study in mice from The Picower Institute and Harvard Medical School finds that in some cases of infection, an immune molecule called IL-17a is released and suppresses a region of the brain's cortex that has previously been linked to social behavioral deficits.

"People have seen this phenomenon before [in people with autism], but it's the kind of story that is hard to believe, which I think stems from the fact that we did not know the mechanism," says Picower Institute member Gloria Choi, the Samuel A. Goldblith Career Development Assistant Professor of Applied Biology at MIT. "Now the field, including my lab, is trying hard to show how this works, all the way from the immune cells and molecules to receptors in the brain, and how those interactions lead to behavioral changes."

Choi and Jun Huh, an assistant professor of immunology at Harvard, are the senior authors of the study, which appeared in *Nature* Dec. 18, 2019. The lead authors are MIT graduate student Michael Douglas Reed and postdoc Yeong Shin Yim.

In 2016, Choi and Huh showed that mice born to mothers who experience infection during pregnancy are more likely to show behavioral symptoms such as deficits in sociability, repetitive behaviors, and abnormal communication. Their research implicated exposure to maternal IL-17a, which produces defects in a specific brain region of the developing embryos. This brain region, S1DZ, is part of the somatosensory cortex.

In the new study, they turned their attention to the link between fever and reduction of autism symptoms. The researchers began by studying mice that exhibited behavioral symptoms due to exposure to inflammation during gestation. They injected these mice with a bacterial component called LPS, which induces a fever response, and found that the animals' social interactions were temporarily restored to normal.

Further experiments revealed that during inflammation, these mice produce IL-17a, which binds to receptors in S1DZ. If the researchers inhibited IL-17a or knocked out the receptors for IL-17a, this symptom reversal did not occur. They also showed that simply raising the mice's body temperature did not have any effect on behavior, indicating that IL-17a, rather than fever, reverses the symptoms.

The team then performed the same experiments in three additional mouse models that lack a gene linked to autism and similar disorders — either Shank3, Cntnap2, or Fmr1. These mice all show deficits in social behavior similar to those of mice exposed to inflammation in the womb, even though the origin of their symptoms is different.

Injecting those mice with LPS produced inflammation, but did not affect their behavior. The reason, the researchers found, is that in these mice inflammation did not stimulate IL-17a production. However, if the researchers injected IL-17a directly into these mice, their behavioral symptoms did improve. This suggests that mice who are exposed to inflammation during gestation end up with their immune systems somehow primed to more readily produce IL-17a during subsequent infections.

Although findings in mice do not always translate into human treatments, the study may help to guide the development of strategies to reduce some behavioral symptoms of autism or other neurological disorders, Choi says.

Neurons that encode reward also extinguish fear

When you expect a really bad experience to happen but it doesn't, it's a distinctly positive feeling. A new study of fear extinction training in mice may suggest why: The findings identify the exact population of brain cells that are key for learning not to feel afraid anymore and show that these neurons are the same ones that help encode feelings of reward.

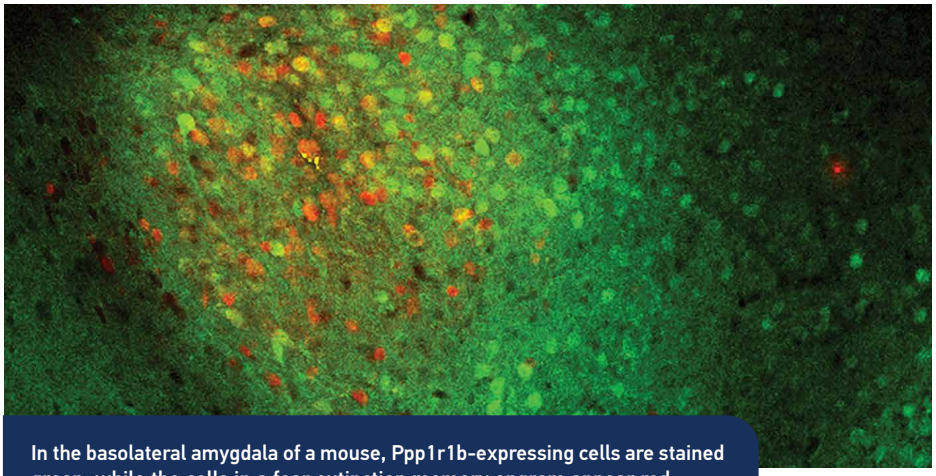
The study, published Jan. 14, 2020, in *Neuron* specifically shows that fear extinction memories and feelings of reward alike are stored by neurons that express the gene Ppp1r1b in the posterior of the basolateral amygdala (BLA), a region known to assign associations of aversive or rewarding feelings, or "valence," with memories. The study was conducted by graduate student Xiangyu Zhang, former graduate student Joshua Kim, and Susumu Tonegawa, Picower Professor of Biology and Neuroscience at RIKEN-MIT Laboratory of Neural Circuit Genetics at The Picower Institute and Howard Hughes Medical Institute.

"We constantly live at the balance of positive and negative emotion," Tonegawa said. "We need to have very strong memories of dangerous circumstances in order to avoid similar circumstances to recur. But if we are constantly feeling threatened we can become depressed. You need a way to bring your emotional state back to something more positive."

In a prior study, Kim showed that Ppp1r1b-expressing neurons encode rewarding valence and compete with distinct Rspo2-expressing neurons in the BLA that encode negative valence.

In fear extinction, an original fearful memory is thought to be essentially overwritten by a new memory that is not fearful. In the study, for instance, mice were exposed to little shocks in a chamber, making them freeze due to the formation of fearful memory. But the next day, when the mice were returned to the same chamber for a longer period of time without any further little shocks, freezing gradually dissipated.

While the mice underwent fear extinction training the scientists watched the activity of the Ppp1r1b and Rspo2 populations in the BLA. They also directly manipulated the populations using optogenetic technology. Their experiments vigorously demonstrated key findings: Ppp1r1b-expressing neurons form specific fear-extinction memory ensembles, or engrams, whose activity suppresses fear memories encoded by Rspo2 neurons; optogenetic activation of Ppp1r1b fear-extinction memory engram cells was as effective as optogenetic activation of Ppp1r1b water reward-activated neurons in driving appetitive behaviors, demonstrating an equivalence between fear extinction and reward.



In the basolateral amygdala of a mouse, Ppp1r1b-expressing cells are stained green, while the cells in a fear extinction memory engram appear red.

Engrams emerge as basic memory unit

The concept of the "engram" as a neural basis for memory is 115 years old but direct evidence for engrams has only begun to accumulate as sophisticated technologies and methods have become available. In a review in *Science* Jan. 3, 2020, Professors Susumu Tonegawa of The Picower Institute and Sheena Josselyn of the Hospital for Sick Children in Toronto describe the rapid progress they and colleagues have been making over the last dozen years in identifying, characterizing and even manipulating engrams, as well as the major outstanding questions of the field.

Experiments in rodents have revealed that engrams exist as multiscale networks of neurons. An experience becomes stored as a potentially retrievable memory in the brain when excited neurons in a brain region such as the hippocampus or amygdala become recruited into a local ensemble. These ensembles combine with others in other regions, such as the cortex, into an "engram complex." Crucial to this process of linking engram cells is the ability of neurons to forge new circuit connections via "synaptic plasticity."

"Evidence indicates that both increased intrinsic excitability and synaptic plasticity work hand in hand to form engrams and that these processes may also be important in memory linking, memory retrieval, and memory consolidation," wrote Josselyn and Tonegawa, Picower Professor of Biology and Neuroscience at the RIKEN-MIT Laboratory for Neural Circuit Genetics and Investigator of the Howard Hughes Medical Institute at MIT.

Importantly, experiments show that the memory initially stored across an engram complex can be retrieved by its reactivation but may also persist "silently" even when memories cannot be naturally recalled, for instance in mouse models used to study memory disorders such as early stage Alzheimer's disease.

For as much as the field has learned, Josselyn and Tonegawa wrote, there are still important unanswered questions and untapped potential applications: How do engrams change over time? How can engrams and memories be studied more directly in humans? And can applying knowledge about biological engrams inspire advances in artificial intelligence, which in turn could feedback new insights into the workings of engrams?

Novel screen offers new Huntington's disease targets

Using a genetic screen that had previously been impossible in the mammalian brain, MIT neuroscientists have identified hundreds of genes necessary for neuron survival. They also identified genes that protect against the toxic effects of a mutant protein that causes Huntington's disease.

"These genes had never been linked to Huntington's disease processes before," said Myriam Heiman, associate professor in The Picower Institute and the Broad Institute of MIT and Harvard, and senior author of the study published Jan. 30, 2020, in *Neuron*. Broad Institute postdoc Mary Wertz is the lead author.

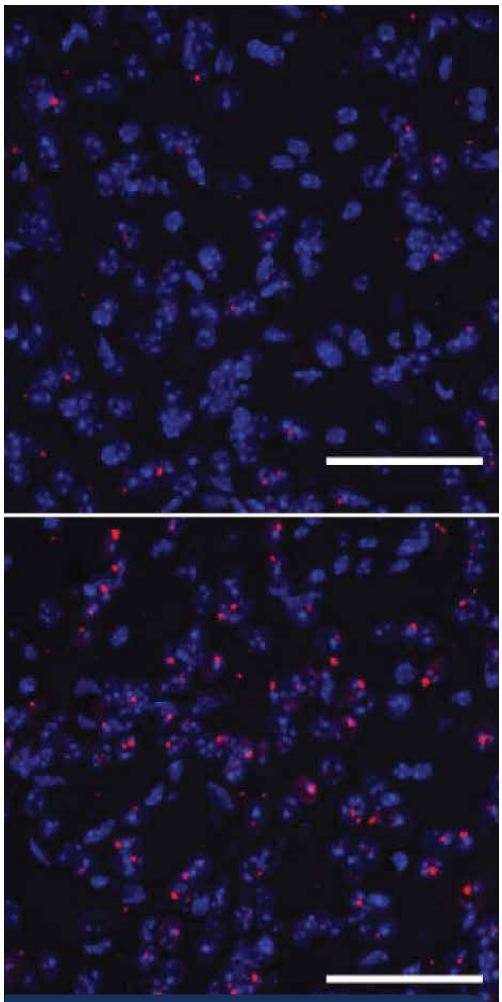
The researchers' new screening technique, which allowed them to assess all of the roughly 22,000 genes found in the mouse brain, could also be applied to other neurological disorders, including Alzheimer's and Parkinson's diseases, Heiman said.

The screening employed libraries of genetic material, shRNAs or CRISPR components, that can be used to turn off the expression of every gene found in the mouse genome. These libraries are delivered by viruses, each of which carry one element that targets a single gene. Heiman's team came up with a way to make their solution of viruses highly concentrated, and to inject them directly into the striatum of the brain.

About seven months after the injection, the researchers sequenced all of the genomic DNA in the targeted striatal neurons. Their approach is based on the idea that if particular genes are necessary for neurons' survival, any cell with those genes knocked out will die. Then, the shRNAs or CRISPR elements will be found at lower rates in the total population of cells. This allowed them to identify genes necessary for neuron survival.

The researchers also screened two different mouse models of Huntington's disease, comparing the results in the Huntington's mice to normal mice. If any of the shRNA or CRISPR elements were found less frequently in the Huntington's mice, that would suggest that those elements targeted genes that are helping to make cells more resistant to mutant huntingtin protein.

The Nme gene family, which has previously been linked to cancer metastasis, but not Huntington's, emerged as a target. The MIT team found that one of these genes, Nme1, regulates the expression of others involved in disposing of proteins. They hypothesize that without Nme1, these genes don't get turned on as highly, allowing huntingtin to accumulate.



When Heiman lab researchers knocked down the gene Nme1, they saw more aggregation of huntingtin protein (in red bottom panel).

Visual memory, amblyopia study yields layers of mystery

In decades of studying how neural circuits in the brain's visual cortex adapt to experience, Professor Mark Bear's lab has discovered cellular mechanisms serving visual recognition memory, in which the brain learns what sights are familiar so it can focus on what's new, as well as a potential therapy for amblyopia, a disorder where children born with disrupted vision in one eye can lose visual acuity there permanently without intervention.

Heading into the experiments described Dec. 17, 2019, in *Cerebral Cortex*, Bear's team expected to confirm that key proteins called NMDA receptors act specifically in neurons in layer 4 of the visual cortex to make the circuit connection changes, or "plasticity," necessary for both visual recognition memory and amblyopia. Instead, the study has produced unexpectedly divergent results.

"There are two stories here," says Bear, who is a co-senior author and Picower Professor of Neuroscience. "One is that we have further pinpointed where to look for the root causes of amblyopia. The other is that we have now completely blown up what we thought was happening in stimulus-selective response potentiation, or SRP, the synaptic change believed to give rise to visual recognition memory."

The cortex is built like a stack of pancakes, with distinct layers of cells serving different functions. Layer 4 is considered to be the primary "input layer" that receives relatively unprocessed information from each eye.

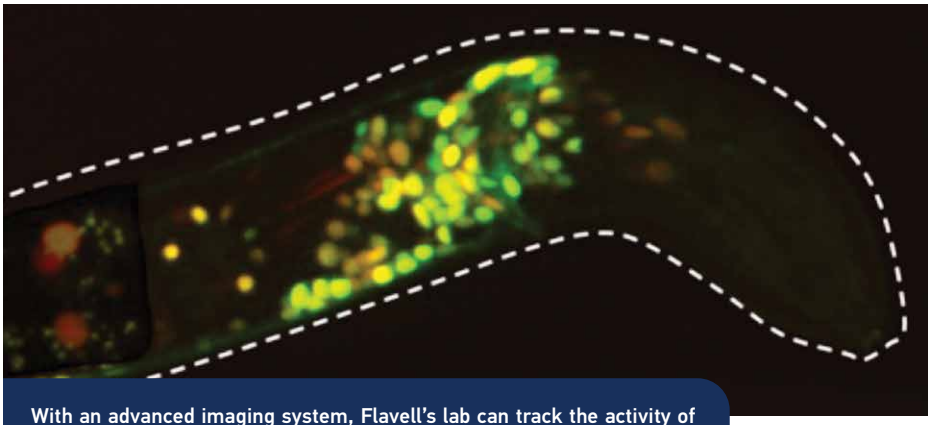
Using a genetic technique to specifically knock out NMDA receptors in excitatory neurons in layer 4 of the visual cortex of mice lead author and postdoc Ming-fai Fong investigated the consequences for visual recognition memory and "monocular deprivation," a lab model for amblyopia in which one eye is temporarily closed early in life.

Her results demonstrated that NMDA receptors in layer 4 neurons are indeed necessary for the degradation of vision in a deprived eye, but apparently play no role in how neural connections, or synapses, serving the uncompromised eye strengthen to compensate, and don't matter for SRP development. That's even though NMDA receptors in visual cortex neurons have directly been shown to matter in these phenomena before, and layer 4 neurons are known to participate in these circuits via telltale changes in electrical activity.

New grant for study of serotonin and behavior

Neuroscientists know little about how the neurotransmitter serotonin affects circuits and behavior in the incredibly complex human brain. To reveal the basics, scientists at MIT's Picower Institute, funded by a new National Institutes of Health grant, will employ a far simpler model: the nematode worm *C. elegans*.

Though it is tiny, transparent and sports a nervous system with only 302 neurons, *C. elegans* is a powerful system for studying how serotonin modulates brain states, said the grant's principal investigator Steven Flavell, Lister Brothers Career Development Assistant Professor. *C. elegans* and mammals share much of the same basic molecular machinery for emitting and receiving serotonin. But unlike in a mammal, all the neurons and their connectivity have been precisely mapped out and scientists can exert powerful genetic control over each cell, including those that express each of the worm's five distinct serotonin receptors. Moreover, Flavell's lab has developed an innovative system that can reliably image the calcium activity of virtually every neuron in real time, even as a worm freely slithers and wriggles around in response to experimental manipulations.



With an advanced imaging system, Flavell's lab can track the activity of many individual neurons in freely moving *C. elegans* worms.

Essentially, Flavell's team can take nearly full control of the worm's serotonergic system and simultaneously observe the response of virtually every neuron in the whole brain. This gives them needed capabilities that aren't available in mammals to figure out how varying patterns of serotonin release can stimulate distinct receptors (or combinations of them) on a multitude of neurons in a variety of circuits to modulate different behaviors.

With the new grant, the lab will pursue three aims: mapping out which combinations of serotonin receptors mediate serotonin's effect on behavior and identifying the exact neurons where they function; analyzing how serotonin alters whole-brain activity; and determining how serotonin-responsive circuits and whole brain activity differs when worms must balance aversive stimuli with appetitive food cues. While the first two sets of experiments will elucidate how the brain deploys serotonin to modulate behavior, the third aim will show how those dynamics change in more complex environments.

"Surprisingly, these fundamental issues related to serotonin signaling remain poorly understood," Flavell said. "Resolving them would greatly enhance our understanding of the serotonergic system."

Scientists eager to explain Alzheimer's advance

The sweeping extent to which increasing 40Hz "gamma" rhythm power in the brain can affect the pathology and symptoms of Alzheimer's disease in mouse models has been surprising, even to the MIT neuroscientists who've pioneered the idea. So surprising, in fact, they can't yet explain why it happens.

In three papers they've demonstrated that exposing mice to light flickering or sound buzzing at 40Hz, a method dubbed "GENUS," strengthens the rhythm across the brain and changes the gene expression and activity of multiple brain cell types. Pathological amyloid and tau protein buildups decline, neurons and their circuit connections are protected from degeneration and learning and memory endure significantly better than in disease model mice who do not receive GENUS.

In a December 2019 review in *Trends in Neurosciences* researchers leading those efforts lay out the few knowns and many unknowns they are eager to understand to determine how the widespread effects take place.

"While we know it affects pathology in mice, we want to understand how because that will help us understand and refine potential treatment," said lead author Chinnakkaruppan Adaikkan, a Picower postdoctoral fellow in the lab of senior author Li-Huei Tsai, Picower Professor of Neuroscience and director of The Picower Institute.

The new paper raises key questions: What cells underlie the brain's response to GENUS? How do gamma rhythms engage non-neuronal cells such as astrocytes and microglia? How does it propagate beyond the brain regions responsible for perception? How extensively can enhancing gamma affect cognition? Does long-term stimulation affect brain circuit connections and how they change?

In his work, Adaikkan is attempting to dissect the roles of specific neuron types in GENUS. But GENUS affects more than neurons. The new paper identifies hypotheses about how supporting "glial" cells are involved.

Also, that GENUS extends to the hippocampus, which is key for memory, and the prefrontal cortex, which is key for cognition, is likely a factor in how it preserves brain function. But again there are competing models for how increased gamma could facilitate multi-regional communication.

"Our lab is excited to tackle these and to see how the field tackles many more," Tsai said. "GENUS has created many intriguing new questions for neuroscience."

Tsai elected fellow of National Academy of Inventors

The National Academy of Inventors has selected MIT neuroscientist Li-Huei Tsai, Picower Professor of Neuroscience and director of The Picower Institute, as a member of its 2019 class of new fellows.

NAI fellows "have demonstrated a highly prolific spirit of innovation in creating or facilitating outstanding inventions that have made a tangible impact on the quality of life, economic development and welfare of society," the organization stated in its announcement Dec. 3, 2019.

Tsai's research focuses on neurodegenerative conditions such as Alzheimer's disease. Her work has generated a dozen patents, many of which have been licensed by biomedical companies including two startups, Cognito Therapeutics and Souvien Bio Ltd., that have spun out from her and collaborator's labs. Her team's innovations include inhibiting an enzyme that affects the chromatin structure of DNA to rescue gene expression and restore learning and memory, and using light and sound stimulation to enhance the power and synchrony of 40Hz gamma rhythms in the brain to reduce Alzheimer's pathology, prevent neuron death and preserve learning and memory. Each of these promising sets of findings in mice are now being tested in human trials.

"The goal of my lab is to improve our understanding of neurodegenerative disease mechanisms and to develop new therapies that could prevent the suffering of millions of people and their loved ones," said Tsai who also directs MIT's Aging Brain Initiative. "A crucial part of that effort is translating promising fundamental findings to the clinic and I'm honored that the NAI has recognized our work toward that goal."

Tsai joins 22 colleagues from MIT as an NAI fellow, including Materials Science and Engineering Department Head Christopher Schuh, who was also elected this year. Among previously elected fellows are Tsai collaborators Emery N. Brown, a fellow Picower Institute faculty member and Edward Hood Taplin Professor of Computational Neuroscience and Health Sciences & Technology, and Ed Boyden, Y. Eva Tan Professor of Neurotechnology.

Picower **People**

MIT HOMEPAGE FEATURES TWO PICOWER INSTITUTE SCIENTISTS

Two Picower Institute researchers, graduate student K. Guadalupe Cruz and postdoc Héctor De Jesús-Cortés, were recently recognized with MIT homepage "spotlights" and in feature articles on MIT News for their extraordinary work to help communities in need. Cruz, who studies the anterior cingulate cortex in the lab of Mriganka Sur, promotes inclusivity of underrepresented minorities at MIT. De Jesús-Cortés, who studies neurodegeneration and the vision disorder amblyopia in Mark Bear's lab, has worked to help Puerto Rico after Hurricane Maria.

Screenshot of a recent MIT homepage.

Héctor De Jesús-Cortés, a Picower Institute postdoc, is working to build a STEM pipeline for students in his native Puerto Rico — including a precollege summer program at MIT. "I want students to be exposed to opportunities," he says.

SIPE EARNS INFINITE KILOMETER RECOGNITION

The School of Science announced that Grayson Sipe, a postdoc in the lab of Professor Mriganka Sur, has earned an Infinite Kilometer Award. Winners are nominated by their peers and mentors for their hard work, which can include mentoring and advising, supporting educational programs, providing service to groups such as the MIT Postdoctoral Association, or some other form of contribution to their home departments, labs, and research centers, the school, and the Institute.

HIGH MARKS FOR LAB SAFETY

The Picower Institute is proud to announce that MIT's Environmental Health & Safety office has recognized the institute with an EHS Excellence Award, based on having at least 90% training completion for FY2019 and for having 95% completion of Level II inspections.

Impact *of* Giving

Jean-Jacques Degroof seeds innovations, including Aging Brain Initiative Alzheimer's research

In his venture investing and philanthropy alike, Jean-Jacques Degroof has the acumen and long-term vision to put innovative ideas on the road to success. He was, for example, an early investor in ZipCar. And when promising results of a non-invasive, sensory-based potential therapy for Alzheimer's disease were emerging in mice in the lab of Picower Professor Li-Huei Tsai, Degroof was among the first partners in advancing it to human studies.

"I know that the first dollars are always the most difficult to raise," he said. "I saw this as an opportunity to make a potential impact by seed funding the project, with the hope that it would then encourage others to join."

Multiple clinical studies of the potential therapy, called "GENUS," are now underway in Tsai's lab in collaboration with Professors Ed Boyden and Emery N. Brown, with Degroof's generous support and that of other donor partners. In her featured talk at the Society for Neuroscience annual meeting in October 2019, Tsai shared some initial data showing that exposing individuals to light flashing and sound buzzing at the 40Hz frequency of "gamma" brain rhythms increases the power and coherence of those rhythms across the brain in people both young and old. In mouse models that same approach has had profoundly positive effects in ameliorating Alzheimer's disease (AD) pathology and symptoms.

"We've been making steady progress toward our goal of determining the effects of GENUS in aging and whether it can help people with AD," Tsai said. "We are so grateful to Jean-Jacques for seeing the potential of these studies and for helping us to get them underway."

EMBRACING ENTREPRENEURSHIP

Born in Belgium, Degroof studied business administration at the Catholic University of Louvain before beginning a career in banking and asset management in New York and Belgium, including the family business, Bank Degroof. He found that he most enjoyed the entrepreneurial side of finance, and decided in his 30s to return to the U.S. to earn an MBA at MIT's Sloan School of Management. He became inspired by MIT's and greater Boston's entrepreneurial climate and stayed for doctoral studies and postdoctoral research focused on promoting university spinoffs and technology transfer in areas with weaker entrepreneurial cultures such as his native Belgium.

Scientists looking to commercialize their work started to approach him for advice. From there he became a venture investor, focusing mostly on biomedical and financial technology startups in the U.S. and Europe.

Jean-Jacques and Valeria Degroof

"Suddenly I realized that helping, supporting, mentoring, coaching and investing in such young spinoff projects was very fulfilling," Degroof said. It took increasingly more of his time relative to academic work, beccoming a full time occupation. Though he left the academic world, Degroof remained a very active MIT alumnus, supporting many programs in aging research, entrepreneurship education and the Mary Rowe Fund, which honors a mentor by promoting research on the future of work.

AGING AND THE LONG TERM

In recent years, Degroof said, he has focused increasingly on philanthropy. He and his wife, Valeria, direct a family foundation, "asbl Jean Degroof – Marcel Van Massenhove," originally established by his father in 1973, focusing on aging. During his tenure, Degroof has structured the foundation's giving to reflect a "venture philanthropy" approach where the foundation seeds innovative programs at academic or charitable organizations and provides up to five years of support in accordance with setting and following a plan and hitting key milestones.

In 2016, with many contacts at MIT and a keen interest in aging issues, Degroof heard about MIT's Aging Brain Initiative and the GENUS research. He got in touch. Attempting to translate such a unique approach to Alzheimer's from mice to people carried some risk, he said, but seemed like exactly the idea he and the foundation could help seed.

"I was willing to take this risk," he said. "So far the results that I am aware of are encouraging."

Degroof says that he has also particularly enjoyed meeting with and helping to support the young scientists involved.

"An important impact is also to make the researchers feel that they are supported and allow them to build a career," he said. "Scientific progress depends on scientists being able to develop and work on long-term research agendas."

Degroof said while he hopes the project will yield a breakthrough, even incremental progress against Alzheimer's would be valuable because there aren't useful treatments.

In philanthropy and business, Degroof relishes helping new ventures get started.

Look and Learn

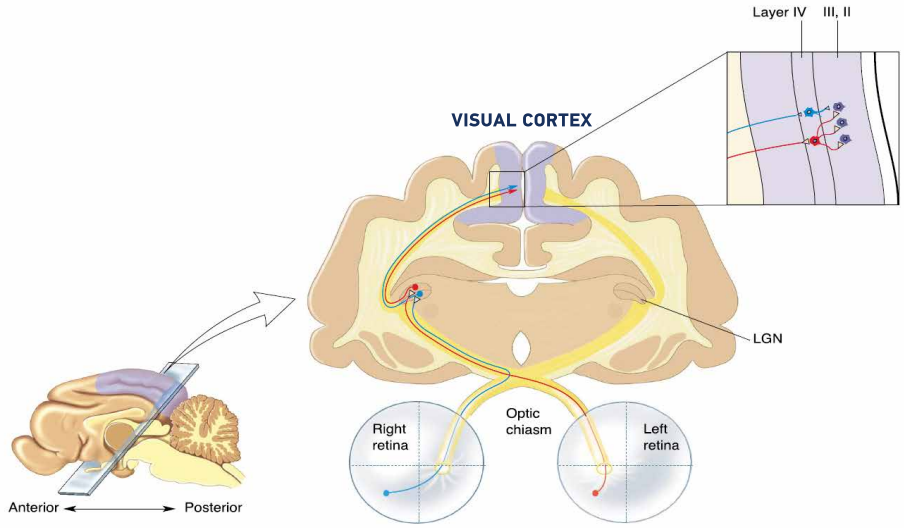
Studying the visual system provides insight into the broader brain

Vision isn't necessary for learning, memory, cognition or behavior, yet studies of how the brain processes sight have produced an extraordinary canon of fundamental insights into all those brain functions. Many of those findings have occurred in labs of The Picower Institute for Learning and Memory, where researchers have put a focus on looking at how the brain looks at the world.

"Many of us are trying to identify principles of cortical function and plasticity that generalize across cortical areas and across species," said Picower Professor Mark Bear.

Bear is one of four Picower Institute professors who've made the visual system integral to their work. In their studies they have probed a pivotal region, the primary visual cortex (V1), and related areas to make major contributions to what the field knows about how neurons and neural circuits change and adapt with experience. That's what Bear means by "plasticity," which is an essential mechanism for learning and memory. Picower scientists have also employed vision in studies of how brain circuits and systems integrate new information into behavior and cognition. In many cases, what they have learned has had important impacts and implications for neurological and psychiatric diseases.

There are many reasons for the special role of the visual system in research on the broader brain. Elly Nedivi, William R. and Linda R. Young Professor, points out that the whole visual system – including the eyes and the optic nerves – is part of the brain, developmentally speaking. They emerge from the "neural tube," the same embryonic structure that produces the brain.



Visual information transmitted down the optic nerve from the retinas is relayed by the LGN to the visual cortex (V1), where it is further processed by circuits among V1's multiple layers. This drawing traces just one point on one side of the visual field. *Image adapted from: Bear, Connors, Paradiso, Neuroscience: Exploring the Brain, 4th edition, with permission.*

"The eyes are the window into your brain," Nedivi said. "It's not just metaphorical."

Vision is our main channel for acquiring experience. In primates, visual processing preoccupies about half the cerebral cortex's total real estate.

Vision is also convenient. Picower Professor Earl Miller and Newton Professor of Neuroscience Mriganka Sur both note that in the lab visual stimulation can be widely varied yet finely controlled. Moreover, because the main inputs to the visual cortex are essentially direct from the eyes, the neural changes and activity observed there are unambiguously relatable to the experimental stimulation. Such responses are easy to measure because the cortex is the brain's surface, so it's fully accessible for imaging or electrical inspection in conscious and responsive animals. Finally, decades of research on V1 in many species make it a well characterized system, making new findings readily interpretable.

SEEING THE BRAIN CHANGE

That history largely began with David Hubel and Torsten Wiesel who produced powerful demonstrations of sensory experience

reshaping the cortex at Harvard in the 1960s and 1970s. If they closed one eye in kittens during the right developmental stage, the kittens lost sight in that eye even after it was reopened and even though the eye remained functional. This paradigm of "monocular deprivation" (MD) and the shift of V1 neurons from serving the deprived eye to the non-deprived eye (called "ocular dominance plasticity," or ODP) inspired neuroscientists to study plasticity in the visual system.

Among them was Bear, who at Brown University in the 1980s collaborated with physicist Leon Cooper, who had co-developed a theory of plasticity. Neuroscientists knew that neural connections called synapses would strengthen with strong input but Cooper's theory predicted they should also weaken with weak input. Moreover, the theory predicted that the threshold of whether input would be weakening or strengthening adjusted depending on overall neural activity – so lower activity lowered the threshold for strengthening vs. weakening.

Bear put the theory into practice. In the 1990s he and his lab members demonstrated the theorized synaptic weakening (called "long-term depression") in V1 and in the hippocampus, a region known for memory. That indicated LTD was a plasticity rule throughout the brain. In 2004 in *Neuron*, Bear's lab, which had moved to MIT, showed that LTD of V1 neurons serving the deprived eye helped explain the degradation of vision in mice subjected to MD. The study also noted that while lid closure caused MD, completely shutting down the retina with a dose of the chemical TTX did not. With no activity at all, visual cortex synapses serving the deprived eye did not undergo LTD.

MD models a common visual disorder called amblyopia in which a cataract or other eye problem during early childhood can lead to ODP, permanently degrading sight through the compromised eye. The typical treatment is to address the occlusion and then patch the good eye to force visual activity to remain with the weaker eye. But patch treatment isn't fully effective and doesn't work after about age 8. Bear and colleagues realized that Cooper's theory and the effects of TTX might yield a better treatment: using TTX to completely, but only briefly, shut down both eyes wouldn't cause LTD, but would lower the threshold for strengthening. When the TTX wore off, V1 synapses for both eyes would be primed for a radical restrengthening. In a study in the *Proceedings of the National Academy of Sciences (PNAS)* in 2016, Bear and collaborators showed exactly that in two different mammal species, even past their period of early development. "Rebooting" the visual system completely restored sight loss triggered by MD. The protocol is not yet clinically applicable, but Bear's lab is building on the results to create one that is. The research, Bear says, shows how a fundamental understanding of plasticity can help rejuvenate neural circuits and activity.

Nedivi's lab has manipulated visual experience in many papers illuminating the fundamental nature of "structural" plasticity, in which synapses don't merely become weaker or stronger but are actually born anew or die away. Last year in *Cell Reports*, for example, she demonstrated that the protein of a plasticity gene she has long studied, CPG15, represents experience to make a newly formed synapse permanent. Synapses come and go, but by manipulating the visual experience of mice and closely tracking individual synapses on V1 neurons, Nedivi's team showed that when a new synapse participates in a circuit responding to experience, it expresses CPG15 and that's what recruits another protein called PSD95 to cement it.

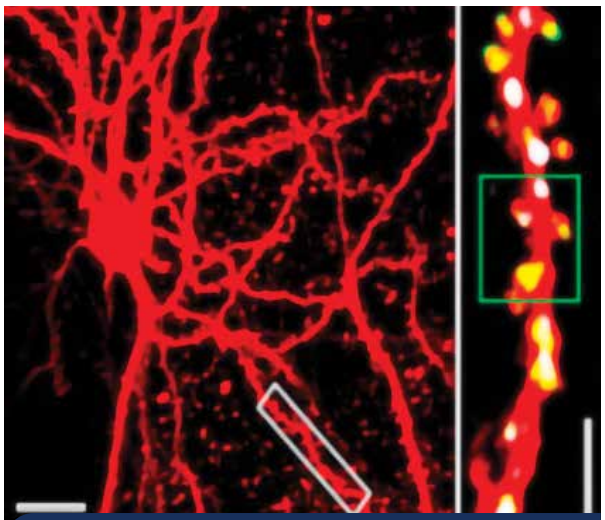
That study focused on synapses that excite their host neurons, but for years Nedivi has also advanced the field's understanding of structural plasticity of both inhibitory neurons and inhibitory synapses, especially in the adult brain where changes are subtle. In 2011 in *Nature Neuroscience*, for example, her lab showed that the first response to MD in the visual cortex is paring down of inhibitory neuron dendrites (neural branches that accept input) and their axonal branches that provide input to other neurons. This reduces inhibition in circuits, which is conducive to a second, constructive phase of new synapse formation. Moreover, the team showed the antidepressant drug fluoxetine could reduce inhibition in much the same way as MD. In a 2018 follow up Nedivi and Bear used modifications of visual experience to show that fluoxetine helped to invigorate the structural plasticity of aging neurons.

Meanwhile back in 2012, Nedivi's keen interest in adult synaptic plasticity produced an important technical advance. Excitatory synapses were easy to track with "two-photon" microscope technology because they always appear on the conspicuous spines that protrude from dendrites. Inhibitory synapses, however, have no such morphological marker. Working with MIT engineer Peter So, Nedivi devised a way to add a second color to two-photon imaging to specifically label and track inhibitory synapses. In *Neuron* the team showed how inhibitory synapses respond to experience by imaging them in V1 as mice underwent visual deprivation. They found that the paring down of inhibitory synapses induced by MD was tightly coordinated with a rearrangement of excitatory synapses on V1 neurons, suggesting local communication between different synapse types.

Sur, too, has employed the visual system to make dramatic findings about plasticity on scales ranging from whole brain regions to individual synapses. In 2000, for instance, his lab showed in *Nature* that in developing ferrets when he disrupted input from the ears to the auditory cortex, the brain repurposed the whole region to become an extension of the visual cortex.

Sur's lab employed MD to discover novel mechanisms underlying weakening of deprived eye synapses and strengthening of non-deprived eye synapses. In several papers, including one with Bear's lab in *Nature Neuroscience* in 2010, another in 2011, and others in the *Journal of Neuroscience* in 2014 and 2018, they showed the mechanisms include activity-regulated genes such as Arc, non-coding RNAs such as microRNAs, and even genes implicated in autism spectrum disorders.

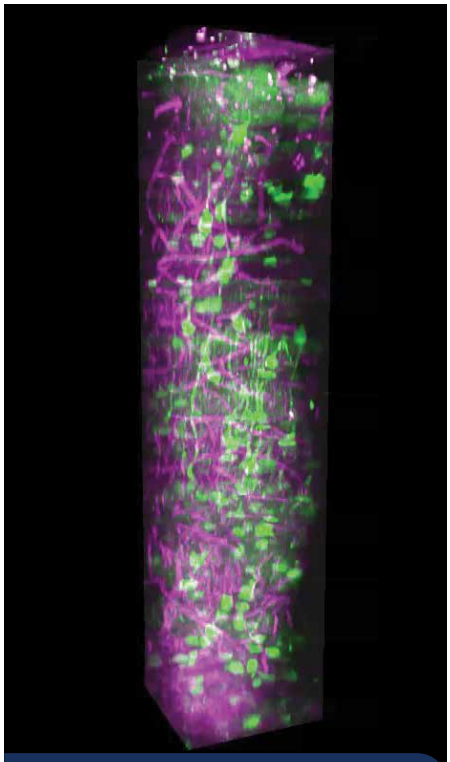
Then, in *Science* in 2018, Sur's team employed sophisticated visual manipulations in mice to identify a new rule of plasticity. Knowing that individual synapses enable neurons to become tuned to exact places within in a mouse's visual field, his lab intervened to shift which synapse responded to stimulation in an exact place to see how the neuron would compensate. He found that as a new synapse strengthened to mark the shift, others nearby quickly weakened.



Elly Nedivi's lab has developed multi-color two-photon microscopy techniques to image multiple synapse types along dendrites in living animals. This figure is from a 2019 paper.

Moreover, they showed that this rebalancing was mediated by the protein arc. Evidence suggests that this compensatory mechanism is likely true well beyond V1, he said.

One of Sur's other fundamental findings about the proteins of synaptic plasticity, based on investigations in V1, has led to a potential therapy for Rett syndrome, a severe autism-like disorder. In 2006 in *Nature Neuroscience* his team published a broad investigation of synaptic proteins with significantly different regulation among developing mice raised in the dark or with MD. A protein called IGF1 stood out. Artificially adding it prevented ODP. As they studied IGF1 more they realized that it promoted synaptic maturation in a way that was missing in Rett syndrome models. In successive papers, for instance in 2009 and 2014, they showed that the protein's activity was repressed by the genetic mutation that causes Rett syndrome, and that giving Rett model mice doses of human IGF1 could help correct problems caused by the mutation not only in the brain, but elsewhere. One of their key assays was observing IGF1's effect in V1 in mutant and control mice. The findings have led to clinical trials of IGF1 for Rett syndrome patients.



In 2019, Mriganka Sur's lab developed a three-photon microscope that could image all the way through the visual cortex of a live mouse.

As with Nedivi, Sur's forays into the visual system have motivated him to drive innovations in microscopy. Two-photon microscopes allow for looking about 0.4 millimeters into the cortex, deeper than traditional optical microscopes, but Sur has sought to observe activity in all six layers of V1, which in a mouse is a millimeter thick. With the technical expertise of So and postdoc Murat Yildirim, Sur's lab advanced three-photon microscopy to the point in 2019 where they indeed imaged neural activity in a live, behaving mouse all the way through a column of V1.

Even before that, Sur's lab in *Science* in 2008 used the columnar organization of visual cortex neurons in V1 of ferrets to show that astrocytes, star-shaped non-neuronal cells, were linked with neurons and also had visual responses. They actively regulated blood flow within the cortex, a mechanism underlying fMRI imaging that relies on blood flow.

PUTTING VISION TO USE

V1, of course, is not just a plasticity proving ground. It's where the brain begins to make sense of what we see. For a long time, neuroscientists thought it might be hardwired to distill features like shapes and spatial orientations but Bear's research has shown it can learn in ways with direct behavioral significance.

In a study in 2006 in *Science* his lab showed that visual cortex neurons learn to predict the timing of a reward. In experiments with mice they paired a flash of light with a later sip of water. At first the neurons only remained active during the flash, but after training they remained active from the time of the flash until the delivery of reward, as if predicting it would come. In another set of studies that continue to this day, his lab has documented that in mice shown the same stimulus repeatedly, V1 neurons show an increased response that allows the brain to characterize the stimulus as familiar, a form of visual recognition memory that may be lacking in some autism patients. In another series of experiments, Bear's team has documented that visual cortex neurons learn whole sequences of stimuli, producing activity patterns attuned to their specific order and timing. The research showed they even anticipate missing members of the sequence.

While these findings have led Bear to joke that V1 may be all the brain needs, of course neuroscientists including Sur and Miller have deeply investigated how visual information flows into the rest of the cortex, which includes many other visual and vision-related areas, to influence behavior and cognition. In a pair of studies in 2016 and 2018, Sur's lab traced neural activity among regions in which rodents had to decide whether to move based on visual stimulation (i.e. like hitting the gas upon seeing a green light). The studies implicated the posterior parietal cortex as the locus where visual input is married with decision-making calculations and output is sent to motor areas. His lab has many other studies underway of the interplay of brain regions in visually guided decision making.

In some of Miller's studies of the large scale patterns of neural activity underlying higher-level cognition, for instance in 2018 in *PNAS*, he has tracked the information processing roles of regions stretching from the visual cortex at the back of the brain all the way to the prefrontal cortex at the front. As lab animals carried out a task that required them to categorize visual stimuli, Miller's team tracked neurons in six regions. Their analysis revealed that even regions with mostly visual responsibilities helped encode information about categorization. They also found that as information moved from sensory to cognitive regions, the dimensionality of the neural activity was reduced. That means that sensory-focused neurons encoded many aspects of the stimuli, but more cognition-related neurons filtered out irrelevant aspects to fixate on fewer properties – the ones relevant to the task – an ability that some with autism sometimes struggle with. But the prefrontal cortex doesn't have to filter. In a seminal study in *Nature* in 2013, Miller and colleagues had also found that when animals were presented with a multifaceted visual discrimination task, prefrontal neurons showed the flexibility to consider as many dimensions of information as was needed, suggesting that neurons aren't hardwired into just one circuit.

That's not to say the brain doesn't have its limits. In studies of how it handles visual information, Miller's lab has found that individuals vary in their ability to process what they see on different sides of their visual field. They have also documented how the brain attempts to simultaneously hold and juggle multiple items of newly acquired sensory information in working memory. A series of studies has revealed that the brain employs specific frequencies of brain waves to hold, use and then discard information based on the requirements of the task at hand. High frequency gamma waves produced in superficial cortical layers encode the new sensory information based on task-informed guidance encoded in lower frequency beta waves from deeper layers. In a study in *Cerebral Cortex* in 2018, though, his lab showed that when the brain tries to store too much visual information, the synchrony provided by these brainwaves breaks down, explaining why working memory capacity is limited.

There are many ways to learn about the brain, but a productive path to insight is through sight.

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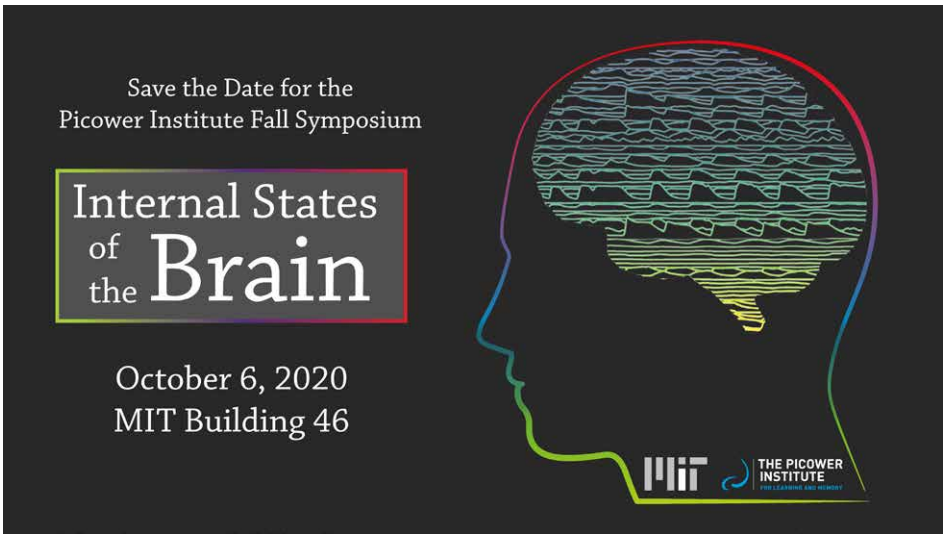
6.02.20
Aging Brain Seminar with Randy Buckner
HARVARD UNIVERSITY

9.17.20
Colloquium with Kang Shen
STANFORD UNIVERSITY

10.01.20
Colloquium with Mathew Diamond
SISSA



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Choi photo by Justin Knight