GENES & DISEASE

Making the long climb from associating a gene with brain disease to developing potential treatments

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Neuroscience News

MIT

WINTER 2020

THE PICOWER INSTITUTE FOR LEARNING AND MEMORY

DIRECTOR'S **MESSAGE**

Dear Friends,

There is no question that 2020 was a trying year, pretty much no matter who you are. Everything is more difficult, and that difficulty is harder to navigate, when we cannot endure it all together. But as best as we can, we have all adapted and persevered.

In this edition's cover story (page 7), we look at a theme in our research that similarly pits determination against difficulty. When scientists are able to associate a gene with disease, either as a cause or a significant risk factor, it rightfully inspires new hope, but a tremendous amount of hard work lays ahead, especially in neuroscience. To translate that knowledge into therapies, researchers must endeavor to understand how alterations in the gene affect the development or degeneration of the brain. This has proven to be no easy task, but several Picower researchers have been able to make important progress, including with several recent studies.

We are not alone. At our Aging Brain Initiative symposium, colleagues from around the world shared key progress against neurodegenerative diseases. You can find a recap on page 10.

In several other stories that follow in our news section we report on other exciting new insights into the brain's extraordinary complexity. We show how DNA opens up to enable memory recall and how neural circuits endow us with the ability to ignore distraction and restrain impulses. We illuminate the role of brainwaves in guiding brain function and describe new ways of imaging the brain. We even describe a new method for understanding how changes in skin conductance reflect changes in the subconscious nervous system, sometimes providing a measure of hidden stress or anxiety.

Our hope is that 2021 offers a new and higher degree of peace and prosperity for everyone. Here's hoping that with continued determination and good fortune we can experience a Happy New Year in the lab and in our lives and do so, once again, together.

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

Neuroscientists discover a molecular mechanism that allows memories to form

When the brain forms a memory of a new experience, neurons called engram cells encode the details of the memory and are later reactivated whenever we recall it. A new study reveals that this process is controlled by large-scale remodeling of cells' chromatin.

This remodeling, which allows specific genes involved in storing memories to become more active, takes place in multiple stages spread out over several days. Changes to the density and arrangement of chromatin, a highly compressed structure consisting of DNA and proteins called histones, can control how active specific genes are within a given cell.

"This paper is the first to really reveal this very mysterious process of how different waves of genes become activated, and what is the epigenetic mechanism underlying these different waves of gene expression," says Li-Huei Tsai, the director of MIT's Picower Institute for Learning and Memory and the senior author of the study.

Asaf Marco, an MIT postdoc, is the lead author of the paper, which appeared in *Nature Neuroscience*.

In the first stage of memory formation, genes known as immediate early genes are turned on in engram cells, but these genes soon return to normal activity levels. Tsai and Marco's team wanted to explore what happens later in the process to coordinate the long-term storage of memories.

They hypothesized that the process could be controlled by epigenomic modifications, which are chemical alterations of chromatin that control whether a particular gene is accessible or not. To study epigenomic changes in individual engram cells over time, the researchers genetically engineered mice to permanently tag engram cells in the hippocampus with a fluorescent protein when a memory is formed. These mice received a mild foot shock that they learned to associate with the cage in which they received the shock. When this memory formed, the hippocampal cells encoding the memory began to produce a yellow fluorescent protein marker.

Right after a memory was formed, the researchers found that many regions of DNA undergo chromatin modifications. In these regions, the chromatin became looser, allowing the DNA to become more accessible. To the researchers' surprise, nearly all of these regions were in stretches of DNA where no genes are found. These regions contain noncoding sequences called enhancers, which interact with genes to help turn them on. The researchers also found that the chromatin modifications did not have any effect on gene expression.

In this mouse brain cross-section, "engram" cells are stained yellow.

The researchers then analyzed engram cells five days after memory formation. As memories were consolidated, or strengthened, over that period, the 3D structure of the chromatin surrounding the enhancers changed, bringing the enhancers closer to their target genes. This still didn't turn on those genes, but it primed them to be expressed when the memory was recalled.

Next, the researchers placed some of the mice back into the chamber where they received the foot shock, reactivating the memory. In the engram cells, the researchers found that the primed enhancers interacted frequently with their target genes, leading to a surge in the expression of those genes.

Many of the genes turned on during memory recall are involved in promoting protein synthesis at the synapses, helping neurons strengthen their connections with other neurons. The researchers also found that the neurons' dendrites — branched extensions that receive input from other neurons — developed more spines, offering further evidence that their connections were further strengthened.

Scientists identify specific brain region and circuits controlling **attention**

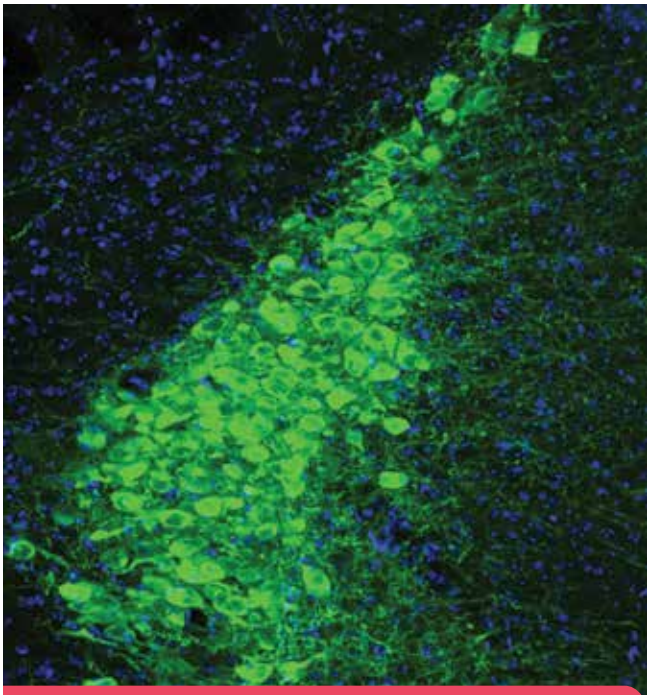
The attentional control that organisms need to succeed comes from two abilities: the focus to ignore distractions and the discipline to curb impulses. A new study by MIT neuroscientists shows that these abilities are independent, but that the activity of norepinephrine-producing neurons in a single brain region, the locus coeruleus (LC), controls both by targeting two distinct areas of the prefrontal cortex.

"Our results demonstrate a fundamental causal role of LC neuronal activation in the implementation of attentional control by the selective modulation of neural activity in its target areas," wrote the authors of the study from the research group of Susumu Tonegawa, Picower Professor of Biology and Neuroscience at RIKEN-MIT Laboratory of Neural Circuit Genetics at The Picower Institute for Learning and Memory and Howard Hughes Medical Institute.

Prior studies have suggested that norepinephrine-producing, or noradrenergic, neurons in the LC might have this role, but the most convincing evidence has been correlative rather than causal, said study lead author Andrea Bari, a research scientist. In the new study in the *Proceedings of the National Academy of Sciences*, the team demonstrated clear causality by using optogenetics to precisely control LC noradrenergic neurons in mice as the rodents engaged in three attentional control tasks. Optogenetics is a genetic technology that allows scientists to control neural activity with flashes of light. The manipulations immediately and reliably impacted the rodents' performance.

The results, the authors said, could aid efforts to understand and treat psychiatric disorders in which attentional control or either of its component abilities is compromised, such as attention deficit and hyperactivity disorder (ADHD).

"ADHD patients may suffer both distractibility and impulsivity," said co-author and research scientist Michele Pignatelli "but you can also have cases mainly characterized by inattentive presentation or by hyperactive-impulsive presentation. Perhaps we can conceive new strategies to tackle different types of ADHD."



Neurons in the locus coeruleus, stained green, are key for controlling attention and impulsive behavior.

Unexpectedly the study also raised new questions about the LC's role in anxiety, Bari said, because to the team's surprise, stimulating LC activity also happened to reduce anxiety in the mice. That's an area for future investigation.

Locus focus

After establishing their method of taking bidirectional optogenetic control of noradrenergic LC neurons—meaning that with different colors of light they could either stimulate or inhibit activity—the researchers tested the effects of each manipulation. In the first task, the rodents had to wait for a half-second flash that signaled which of two portals held a food reward. Mice in whom LC neurons were optogenetically stimulated did the task correctly more often and made fewer premature moves than when not manipulated. Mice whose LC neurons were inhibited did the task correctly less often (less attention meant missing that light flash) and jumped the gun more often.

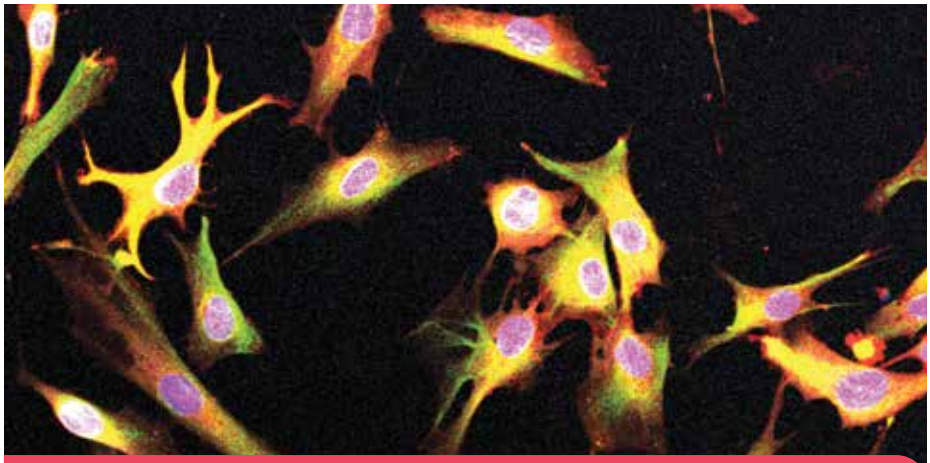
In the second task, before seeing the light that flagged the reward portal (this time for three seconds), the mice saw a "cue" flash. Sometimes that cue would be on the opposite side, sometimes in the middle and sometimes on the correct side. Again LC stimulation improved correctness and suppressed impulses while inhibition reduced correctness and increased impulses. Importantly, stimulated-LC mice showed no difference in reaction time regardless of cue position because they were focused on the reward goal. But reaction time varied in inhibited-LC mice because they were distracted by the cue—when it was on the wrong side they found the portal more slowly than normal and when the cue was on the correct side they reacted faster.

In task three, the mice faced the possibility of constant distraction by irrelevant lights while they waited for the three-second signal of the food reward location. The same results ocurred, with one exception. When there were no distractors, with three long seconds to notice the signal, inhibited-LC mice did not lapse in performing correctly. They only showed the deficit amid distractors.

To test whether attentional focus and impulse control were independent, the team controlled LC activity and norepinephrine release not at the main neuron bodies as before, but now only where their long projections connected to specific areas of the prefrontal cortex (PFC). Going on some of Bari's prior research and other hints, they targeted the dorso-medial PFC (dmPFC) and the ventro-lateral orbitofrontal cortex (vlOFC). Stimulating LC connections into the dmPFC increased correct performance but did not reduce premature responses. Meanwhile, stimulating LC connections in the vlOFC did not improve correct performance, but did reduce premature responses.

"Our results reveal that the attentional control of behavior is modulated by the synergistic effects of two dissociable coeruleo-cortical pathways, with LC projections to dmPFC enhancing attention and LC projections to vlOFC reducing impulsivity," the authors wrote.

Alzheimer's risk gene disrupts endocytosis, but another disease-linked gene could help



Astrocytes are a key type of brain cell. A new study shows how Alzhemer's risk genes affect their function.

Scientists at The Picower Institute and the Whitehead Institute have found evidence that the most prominent Alzheimer's disease risk gene may disrupt a fundamental process in a key type of brain cell. Moreover, in a sign of how important it is to delve into the complex ways that genes intersect in disease, they found that increasing the expression of another Alzheimer's-associated gene in those cells could help alleviate the problem.

Scientists have been working for decades to understand why the *APOE4* gene variant substantially increases Alzheimer's risk. The new study in *Cell Reports* finds that in astrocytes, which are the most common non-neuron cell in the brain, the variant hampers the process of endocytosis, which is a major way that cells bring materials in from outside. That functional deficit could undermine several of the vital roles that astrocytes play in the brain.

The study's co-lead authors are Grzegorz Sienski of the Whitehead Institute and Priyanka Narayan, a researcher at the National Institutes of Health who co-led the work while a postdoc in the lab of the late Susan Lindquist and then the lab of Li-Huei Tsai, Picower Professor of Neuroscience.

By comparing lab-cultured human astrocytes that were identical except in whether they had the *APOE4* or *APOE3* variants, the researchers found several signs of disrupted endocytosis, specifically in the early stage of the process when key proteins were notably reduced in the *APOE4*-carrying cells. They were able to directly observe that the afflicted astrocytes were less capable of bringing in materials from the outside.

The team modeled the *APOE4* endocytosis deficit in yeast cells and used those to screen for proteins that might provide a protective effect. They found that expressiong an analog of a human gene called *PICALM* improved *APOE4* cells' endocytosis. When the scientists overexpressed *PICALM* in *APOE4* human astrocytes, it repaired early endocytosis function, as measured by the increased intake of test proteins.

"Both *APOE* and *PICALM* are Alzheimer's risk genes," Tsai said. "It is really interesting that the two genes converge on endocytosis. This indicates that faulty endocytosis plays a key role in the etiology of Alzheimer's."

As information flows through brain's hierarchy, higher regions use higher frequency waves

Your brain processes information in a hierarchy of regions along its surface, or cortex, ranging from "lower" areas that parse incoming sensations to "higher" executive regions that formulate plans. MIT neuroscientists seeking to explain how this organization emerges report two broad trends: In each of three distinct regions, information encoding or its inhibition was associated with a similar tug of war between specific brain wave frequency bands, and the higher a region's status in the hierarchy, the higher the peak frequency of its waves in each of those bands.

The team's new study in the *Journal of Cognitive Neuroscience* provides a unifying view of how brain waves may control the flow of information up and down the hierarchy.

"We wanted to obtain an overarching picture so that's what we did," said Earl Miller, Picower Professor of Neuroscience and senior author of the study. "We addressed the question of what does this look like all over the cortex."

Picower Institute postdoc Andre Bastos and Mikael Lundqvist of Stockholm University and MIT are the study's co-first authors.

In the visual cortex, the parietal cortex and the prefrontal cortex they found that when animals first saw an image or recalled that image in a later test, the power of theta and gamma frequency bands of brain waves would increase in bursts and power in alpha and beta bands would decrease. When the image had to be held in mind, theta and gamma power went down and alpha and beta power went up in bursts.

While this pattern applied across all three regions, a key difference was that each region employed a distinct peak within each frequency band. While the visual cortex beta band, for instance, peaked at 11 Hz, parietal beta peaked at 15 Hz and prefrontal beta peaked at 19 Hz. Meanwhile visual cortex gamma peaked at 65 Hz, parietal gamma topped at 72 Hz and prefrontal gamma at 80 Hz.

"The increased frequency in the oscillatory rhythms may help sculpt information flow in the cortex," the authors wrote.

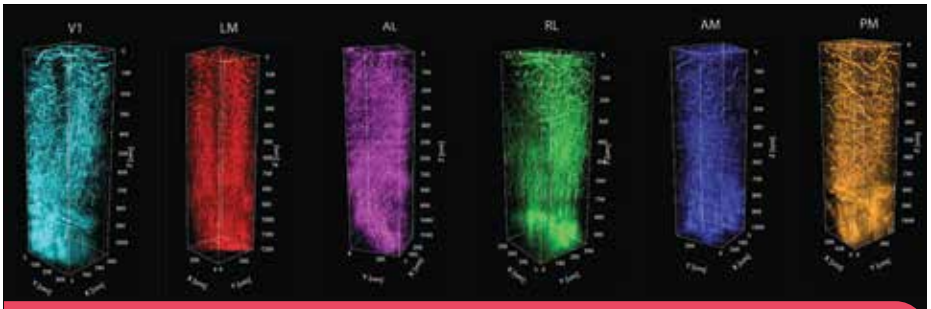
Live imaging method brings structural information to mapping of brain function

Scientists distinguish brain regions by what they do, but have lacked a way to overlay information about how they are built, especially in live animals while they are performing the functions of interest. Now MIT researchers have produced an unprecedented pairing of functional mapping in live mice with distinguishing structural information for each region.

"Our study shows for the first time that structural and functional coupling of visual areas in the mouse brain can be detected at sub-cellular resolution *in vivo*," wrote the authors based in the lab of Mriganka Sur, Newton Professor of Neuroscience in The Picower Institute.

The technique could give scientists more precise ways to distinguish the borders and contents of regions they wish to study, helping them better understand how structural distinctions develop within individuals in different functional regions over time. Sur's lab, for instance, is intensely interested in understanding the development of the visual system, which involves many brain areas.

"There is something profound in the way that vision is represented and created in mammalian brains," Sur said. "Where do these areas come from, what do they mean and what do they do? The critical thing is to precisely map or match the functional representation of each area with its anatomical uniqueness."



Six different regions in the visual cortex of a mouse show distinct anatomy of blood vessels and myelin fibers.

To develop tools to help answer those questions, postdoc Murat Yildirim led the research published in *Biomedical Optics Express*. The team combined a method of charting functional areas—retinotopic mapping—with deep structural information measured by a technology Yildirim has helped to pioneer—third-harmonic generation (THG) three-photon microscopy.

In retinotopic mapping, researchers can identify functional regions by engineering neurons to flash when they become electrically active (and show changes in calcium) in response to a particular stimulation. Three-photon microscopy can finely resolve individual cells and their smaller substructures as deep as a millimeter or more—enough to see all the way through the cortex. THG, meanwhile, adds the capability to finely resolve both blood vessels and the fibers of a material called myelin that wrap the long, tendrilous axons of many neurons. This allowed them to discern unique structural attributes for each region.

Statistical model improves analysis of skin conductance

Electrodermal activity – the sweat-induced fluctuations of skin conductance made famous in TV dramatizations of lie-detector tests – can strongly indicate subconscious, or "sympathetic," nervous system activity, but only if it is analyzed optimally. In the *Proceedings of the National Academy of Sciences*, an MIT-based team of scientists provides a new, fast and accurate statistical model for analyzing EDA.

Existing methods either compute averages of the signal that obscure its instantaneous nature or inefficiently force measurements into a fit with signal processing models that have nothing to do with what's going on in the body.

To make EDA analysis faster and more accurate for interpreting internal cognitive states (like anxiety) or physiological states (like sleep), the research team sought a model to match the actual physiology of sweat. When stimulated by the sympathetic nervous system, glands under the skin build up a reservoir of sweat and then release it when they are full. This kind of process, called "integrate-and-fire," is also characteristic of natural phenomena like the electrical spiking of nerve cells and geyser eruptions, said senior author Emery N. Brown, Edward Hood Taplin Professor at The Picower Institute.

Sandya Subramanian, a graduate student in the Harvard-MIT Health Sciences and Technology program is the study's lead author.

Brown and Subramanian recognized that there is a well-established statistical formula for describing integrate-and-fire systems called an "inverse Gaussian."

The researchers formulated an inverse Gaussian model of EDA and then put it to the test with 11 volunteers who wore skin conductance monitors for an hour as they sat quietly, read or watched videos. Even while "at rest" people's thoughts and feelings wander, creating variation in the EDA signal. The inverse Gaussian produced a tight fit with the readings in all 11. In 9 of the 11 cases, adding one of a few related statistical models tightened the inverse Gaussian's fit a little further.

Subramanian said that in practical use, an EDA monitoring system based on an inverse Gaussian model alone could immediately be useful, but it could also be quickly fine-tuned by initial readings from a subject to apply the best combination of models to fit the raw data.

New trial to test brain wave stimulation as Alzheimer's preventative

Wth a new $1.8 million grant from the Part the Cloud-Gates Partnership Grant Program of the Alzheimer's Association, researchers at Massachusetts Institute of Technology and Massachusetts General Hospital are launching a new clinical trial to test whether stimulating a key frequency of brain waves with light and sound can prevent the advance of Alzheimer's disease pathology even before volunteers experience symptoms such as memory impairment.

"Because Alzheimer's disease leads to neurodegeneration and cognitive decline, the best time for intervention may be before those symptoms even begin," said Li-Huei Tsai, Picower Professor of Neuroscience and director of The Picower Institute for Learning and Memory at MIT. "We are hopeful that our safe, non-invasive approach of sensory stimulation of 40Hz gamma brain rhythms can have a preventative benefit for patients. We are very grateful to Part the Cloud-Gates Partnership Grant Program for their support in funding rigorous research to test this exciting possibility."

In extensive testing with multiple mouse models of Alzheimer's, the light and sound stimulation technique, called Gamma ENtrainment Using Sensory Stimuli (GENUS), improved cognition and memory, prevented neurodegeneration, and reduced amyloid and tau protein buildups. The research showed that increasing 40Hz brain rhythm power and synchrony stimulated the brain's immune cells and its blood vessels to clear out the toxic proteins. Early results from human testing at MIT show that GENUS is well tolerated and increases 40Hz power and synchrony, just like in the mice.

The new study, conducted in collaboration with neurologist Keith Johnson at MGH, will enroll 50 volunteers aged 55 or older who show signs of amyloid protein plaque buildup in PET scans but who remain cognitively normal.

Brown wins SfN's Swartz Prize

The Society for Neuroscience announced Oct. 26 that it has awarded the Swartz Prize for Theoretical and Computational Neuroscience to Emery N. Brown, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience at MIT.

Brown, a member of The Picower Institute and the Institute for Medical Engineering and Science, is a neuroscientist, a statistician and a practicing anesthesiologist at Massachusetts General Hospital and Harvard Medical School. His research has produced principled and efficient new methods for decoding patterns of neural and brain network activity and has advanced neuroscientific understanding of how anesthetics affect the brain, which can improve patient care.

"Dr. Brown's seminal scientific contributions to neural signal processing and the theory of anesthetic mechanisms, together with his service as an educator and a physician, make him highly deserving of the 2020 Swartz Prize," SfN President Barry Everitt said in a press release announcing the award. "Dr. Brown has demonstrated an unusually broad knowledge of neuroscience, a deep understanding of theoretical and computational tools, and an uncanny ability to find explanatory simplicity lurking beneath complicated observational phenomena."

Brown said the recognition made him thankful for the chances his research, teaching and medical practice have given him to work with colleagues and students.

"Receiving the Swartz Prize is a great honor," he said. "The prize recognizes my group's work to characterize more accurately the properties of neural systems by developing and applying statistical methods and signal processing algorithms that capture their dynamical features. It further recognizes our efforts to uncover the neurophysiological mechanisms of how anesthetics work and to translate those insights into new practices for managing patients receiving anesthesia care.

Emery N. Brown speaks at the 2019 Society for Neuroscience annual meeting.

"Finally," he added, "receipt of the Swartz Prize makes me eternally grateful for the outstanding colleagues, graduate students, post-docs, undergraduates, research assistants and staff with whom I have had the good fortune to work."

Picower researcher earns BBRF Young Investigator grant

Vincent Breton-Provencher, a postdoc in the lab of Newton Professor of Neuroscience Mriganka Sur, is among a select group of promising researchers to be awarded Young Investigator grants, The Brain & Behavior Research Foundation announced this fall.

Breton-Provencher is working to understand the neurobiology of attention to better diagnose ADHD and disruptive behavior, and to develop potential treatments. To do so he studies the neurotransmitter noradrenaline (NA) in a brain region called the locus coeruleus (LC), specifically looking at circuits connecting the LC to the motor and prefrontal cortices, and their involvement in sustained attention and cognitive flexibility. His experiments will seek to determine how NA activity affects cortical computations in neurons during attention, which could aid in understanding the heterogeneity of ADHD dysfunctions.

"I am very honored to be receiving the Young Investigator Award from BBRF, which will support my research on the role of noradrenaline in learning and attention that I am currently conducting at MIT," Breton-Provencher said. "As I am about to start my own lab by the summer of 2021 at the Université Laval in Québec City, the award will also be a tremendous help for this transition period."

GENES & DISEASE

Picower scientists are making the dauntingly long but highly motivating climb between associating a gene with disease and developing potential treatments.

DNA's resemblance to a twisted ladder provides an apt metaphor. Identifying a specific gene as the cause of disease or as a significant risk factor gives researchers clear direction toward developing treatments, but it also puts them at the bottom rung of what history has shown to be a long climb. Undeterred, several Picower Institute labs have embraced the challenge of turning genetic knowledge into the neuroscience needed to produce clinical advances for developmental, psychiatric and neurodegenerative brain disorders.

Their goal is to pinpoint *how* a genetic aberration undermines the function of brain cells and circuits. Learning how things go wrong puts within reach new ideas for preventing or reversing those problems. Indeed some strategies developed at the Picower Institute have advanced potential therapies all the way to clinical trials.

"Discovery of the gene is just the first step in a mechanism-based understanding and it can take decades," says Mriganka Sur, Newton Professor of Neuroscience. Sur is a global leader in studying how mutations in the gene *MECP2* hinder the development of neurons and neural circuits and the maturation of neural connections, called synapses, disrupting intellectual development in patients with Rett Syndrome, an autism-like disorder.

Because the brain is a uniquely complex system that constantly adapts and changes, diseases of the central nervous system can be especially tricky to understand mechanistically, especially when their pathology plays out over the course of decades, said Myriam Heiman, Associate Professor in the Picower Institute and the Broad Institute of MIT and Harvard.

In the early days of the Human Genome Project many people hoped that identifying genes would make finding treatments straightforward. Sometimes this is possible. In the brain-affecting metabolic disease PKU, for instance, identifying the genetically inherited loss of ability to regulate the biochemical phenylalanine led to a clear therapeutic strategy of restricting diet (though a cure remains undiscovered).

"But many diseases of the nervous system don't follow that paradigm," said Heiman, who this year has published two papers in *Neuron* finding novel mechanisms and potential therapeutic targets in Huntington's disease, a fatal and incurable neurodegenerative disorder. Scientists have known for more than 25 years that just one type of mutation—an accumulation of repeating CAG trinucleotides in the *Huntingtin* gene—causes toxic aggregation of Huntingtin protein, but as Heiman's new research shows, there is still a lot to learn about how that makes neurons vulnerable.

Genetic cause

Picower Professor Mark Bear has been waging a battle against Fragile X syndrome, the leading heritable cause of intellectual disability and autism, for nearly 20 years. Fragile X is caused by mutation—specifically CGG nucleotide repeats—in the *FMR1* gene that can eliminate production of the protein FMRP. As such it is a "simple" disease, Bear says.

"We actually know the cause," he says. "We don't have to guess about it. All that goes wrong in individuals with Fragile X syndrome is due to the absence of this FMRP protein."

The work started back in 2002 with a paper in the *Proceedings of the National Academy of Sciences* (PNAS). In fundamental research on mechanisms of synaptic plasticity—the way neurons change their circuit connections in response to experience to enable development, learning and memory—Bear's lab discovered that loss of FMRP exaggerates the consequences of activating a neurotransmitter receptor called metabotropic glutamate receptor 5, or mGluR5. Activating mGluR5 causes synapses to weaken, a normal process called long-term depression, but without the brake provided by FMRP, there is too much LTD.

[Mark F. Bear]

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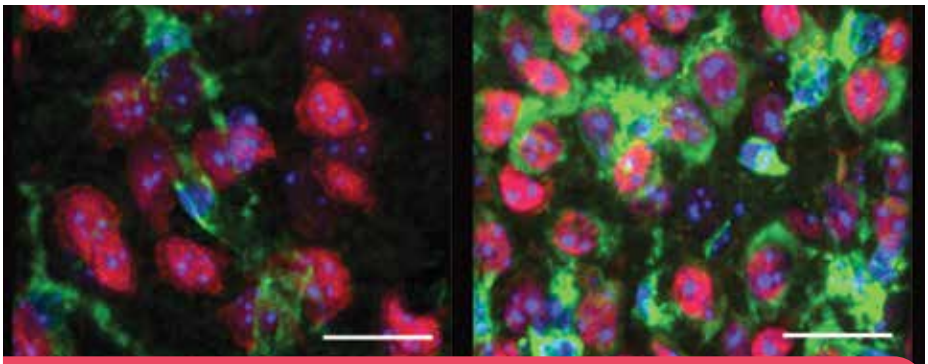
With this mechanistic insight, Bear's lab hatched a strategy of treating Fragile X by inhibiting mGluR5. They showed in *Neuron* in 2007 that it was enormously effective in mouse models and eventually brought a candidate drug to advanced clinical trials, but it fell short of meeting the clinical goals set by regulators.

Undaunted, earlier this year Bear's team published a new study in *Science Translational Medicine* (STM) demonstrating a promising updated approach. Study data indicated that one potential problem was that patients could build up a tolerance to the mGluR5 medicine. So Bear's lab pursued another target in the mGluR5 pathway: the enzyme GSK3-alpha. Working with scientists at the Broad Institute, they tested a new drug to inhibit the enzyme, which is overactive in Fragile X mouse models, and found that doing so successfully reversed several symptoms. The drug showed no concerning side effects in the mice and the rodents did not build up tolerance.



Huntigton's disease neurons in the right panel show high levels of PKR (stained green), indicating immune response to mitochondrial RNA, compared to normal controls (left panel).

"We don't know whether the mGluR5 trials failed because of treatment resistance, but it's a viable hypothesis," Bear says. "What we do know is with the GSK3 alpha inhibitor, we do not see that in mice."

Sur's quest to treat Rett syndrome has some parallels with Bear's experience. He, too, happened upon a promising treatment strategy by performing fundamental research on synaptic plasticity (which is a core research theme at The Picower Institute).

[Mriganka Sur]

MECP2's protein regulates the expression of hundreds of other genes. In *Nature Neuroscience* in 2006, Sur's lab discovered evidence that a protein called IGF1 is a crucial component in how synapses in the visual cortex in newborn mice develop in response to visual activity. IGF1 is regulated by MeCP2 and is indeed notably reduced in mouse models of Rett Syndrome. Sur's lab has shown that the lack of IGF1, in turn, reduces levels of proteins such PI3K/Akt, and that undermines still other proteins needed for synapses to strengthen and mature properly. In a paper in 2014 in *PNAS* the team showed that treating mice by dosing them with IGF1 corrects functional, structural, and molecular mechanisms downstream of MeCP2 and improves mouse behavior. Since then, the idea has been tested in Rett syndrome patients in clinical trials. One trial did not show sufficient efficacy, but another phase III study is still pending.

Sur's lab has not stopped working on the problem. Several lab members continue to study how the gene regulation and expression cascade that depends on MeCP2 affects neural development, not only in mice but also in complex 3D models of human brain tissue called cerebral organoids. And in *STM* last year, Sur collaborated with MIT biologist Rudolf Jaenisch of the Whitehead Institute to show that increasing expression of another key protein in the cascade, KCC2, also provided therapeutic benefits in mouse models, offering a fresh lead.

"Nothing has worked in patients yet, but you know we have to keep trying," Sur said. "It's a very hard problem. It goes to the heart of how the brain is made, which is a very complex process."

So, as it turns out, is the process by which the brain is unmade in neurodegenerative disorders such as Huntington's disease.

In her work to understand the mechanisms by which the *huntingtin* mutation leads to the deaths of specific neurons in a brain region called the striatum, Heiman has been using new, unbiased techniques to study the brains of Huntington's disease patients and also those of mouse models of the disease. Unbiased means she isn't confining her studies to prior hypotheses because doing so would be to assume that the field already knows everything that's going wrong. But in diseases of the aging brain, it is very hard to fully understand the drivers of disease pathology, Heiman said. Decades of damage and compensation can obscure underlying mechanisms. She likens it to examining an unprotected crime scene.

[Myriam Heiman]

"There have been many mechanisms put forward in the past, but they haven't been successful in clinical trials," Heiman said.

In January she published a study in which her lab knocked out all 22,000 genes found in the mouse striatum in a way in which any given cell had only about one gene knocked out. No one had ever accomplished this feat before in a mammal's brain, but by doing so Heiman's team was able to learn which genes are necessary for neurons to survive. When her team did the screen in Huntington's disease model mice, they identified a particular gene family, called *Nme*, that had never been associated with Huntington's before, but which was clearly necessary for neurons to survive the disease. The gene, as it turns out, may help cells dispose of protein aggregates (such as mutant Huntingtin). Heiman's team showed that when *Nme1* is overexpressed in the mouse models of Huntington's, disease symptoms appear to improve.

Then in July, Heiman's lab produced another study based on unbiased profiling of gene expression in striatal neurons known to be vulnerable in the disease. In this case, the researchers looked at gene transcription and translation (as measured by levels of RNAs) in different types of cells in both human and mouse brains. Across both species, and across different stages of the disease, they found that RNA from mitochondria were misplaced in striatal cells, called spiny projection neurons, that are particularly vulnerable to dying. They found evidence that the brain cells were perishing amid an immune response to the errant mitochondrial RNA, which looked to the cells like a viral invader. This insight offers another new mechanism of Huntington's pathobiology that could be targeted in the future.

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Genetic risk factors

On the other side of the Picower Institute's fourth floor, Picower Professor and Institute director Li-Huei Tsai is hunting for therapies for a different neurodegenerative disease: Alzheimer's. Her lab takes many approaches, but among them is understanding the mechanistic failures brought about by the disease's single biggest genetic risk factor, the *APOE4* variant of the *APOE* gene.

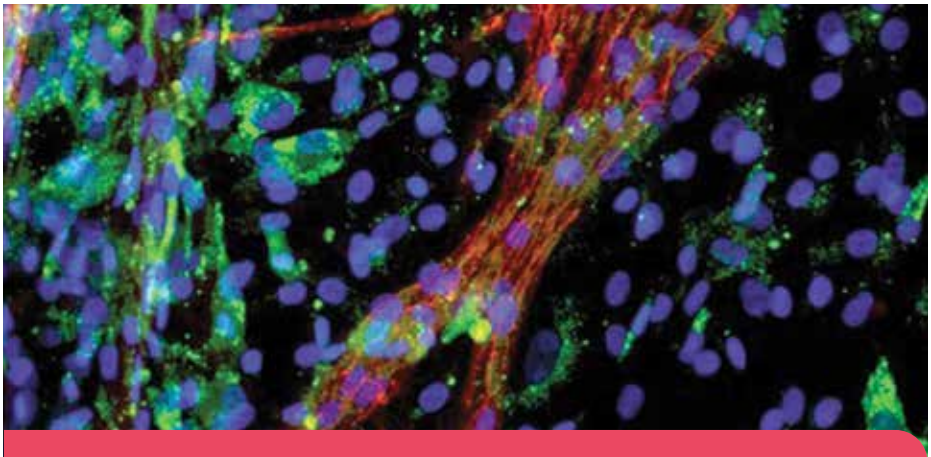
As with autism spectrum disorders, the vast majority of Alzheimer's cases cannot be traced to a clear inherited genetic cause (Fragile X and Rett syndromes are exceptions). Instead, most Alzheimer's is associated with variations in many genes, which are not causal but appear to convey extra risk. For that information to be useful, scientists need to what effect the variations have.

Over the last few years, Tsai's lab has revealed several things that go wrong in brain cells carrying *APOE4* vs. the more common *APOE3* version. In 2018, they used stem cells derived from patients' skin cells to create cultures of key brain cell types: neurons, microglia and astrocytes. In *Neuron* the team showed that *APOE4* neurons secreted more amyloid protein, a hallmark of Alzheimer's pathology, than *APOE3* neurons. Meanwhile, *APOE4* astrocytes and microglia showed less ability to remove amyloid.

[Li-Huei Tsai]

In a study earlier this year in *Nature Medicine*, Tsai's lab used similar techniques to engineer *APOE3* and *APOE4* versions of the blood-brain barrier (BBB), the security fence that keeps unwanted pathogens or chemicals from entering the brain. The BBB is almost always disrupted in Alzheimer's by a strongly correlated condition called Cerebral Amyloid Angiopathy. Tsai's team was able to show that *APOE4* made the BBB more vulnerable particularly because of disrupted functioning among specific vascular cells called pericytes. The scientists went on to identify the specific mechanistic pathway that becomes errant and that it can be corrected with specific medications.

A few months later, Tsai's lab published yet another set of findings about *APOE4*'s ill-effect in the brain. They showed that astrocytes with *APOE4* appeared to struggle with the crucial process of endocytosis, a major means by which the cells bring material into their bodies, which in turn can undermine how they support healthy brain function. This study took a hopeful turn, however, by showing that overexpression of another Alzheimer's associated gene, *PICALM*, corrected the defect.



Tsai lab researchers created a blood-brain barrier model in the lab. With the APOE4 gene variant, vessels accumulated a lot of amyloid protein (green).

Not only was the study an important advance in understanding how *APOE4* may undermine brain function, and maybe how to treat it, but also it highlighted the value of an emerging strategy in studying Alzheimer's disease and assessing it in patients: polygenic risk. Scientists are beginning to realize that they need to know how genetic variants may combine and accumulate to affect disease risk for patients, Tsai said.

"It's a concept people have talked about for a long time, but I think now people are finally beginning to think seriously about how to work on it," Tsai said. "Someone's risk for developing Alzheimer's is probably to a large part based on their genetics—how many risk alleles they carry."

The same is likely true in bipolar disorder, said Elly Nedivi, William R. and Linda R. Young Professor of Neuroscience in the Picower Institute. In 2019 in *Molecular Psychiatry*, she showed how single and combinations of variants in the gene *SYNE1* appear to undermine the ability to regulate synaptic strength in bipolar disorder.

[Elly Nedivi]

However, none of these variants which affect expression or function of CPG2, a key protein encoded by *SYNE1*, are sufficient to outright cause bipolar disorder on their own. Instead they likely increase a susceptibility that is influenced by many factors – much like family history contributes to the chance of developing heart disease, but is not deterministic on its own.

"It's a risk—its something that's against you, but the question is what else do you have going for you?," Nedivi said. "The constellation of *SYNE1* variants in combination with the rest of your genetic makeup, as well as other factors in your life will determine together whether you will develop the disease."

Nedivi's lab discovered CPG2 while screening neurons for proteins whose expression depends on synaptic activity. Their 2004 study in *Neuron* revealed that CPG2 is expressed in an area right next to excitatory synapses that helps to traffic receptors for the neurotransmitter glutamate to the synapse. As such, it is important for helping synapses adapt to activity levels by adding or removing these receptors. In the 2019 study, Nedivi's research team identified several *SYNE1* variants in people with biopolar disorder and tested the effect of these variants on CPG2 level or function in rat neurons. They found that the different genetic aberrations undermined CPG2 in various ways— by reducing its expression, or attenuating its ability to regulate glutamate receptor trafficking, particularly in response to changes in synaptic transmission, when it's most needed. The study was the first to connect the finding of genetic factors in bipolar to a specific physiological mechanism in the brain.

Nedivi's lab is following up on the findings. This fall she hired a new postdoctoral researcher to continue this work, in particular to test whether the detrimental affects of bipolar patient mutations in CPG2 can be counteracted pharmaceutically. "I love this project," Nedivi said. "I think it has enormous potential for both therapeutics, as well as diagnostics."

After all, as in the other ongoing efforts of Picower Institute researchers, it represents the rewarding possibility—even if it's a steep climb—of going from identifying genes, to developing neuroscientific understanding, to treating devastating diseases.

Symposium highlights numerous leads to combat neurodegeneration

Picower Clinical Fellow Diane Chan, a neurologist in the Tsai lab, discusses human testing of sensory light and sound stimulation to prevent or treat Alzheimer's disease.

The neuroscientists who spoke at MIT's Aging Brain Initiative symposium, "Molecular and Cellular Mechanisms of Neurodegeneration" Sept. 22 delved deep into the complexities of devastating brain diseases such as Alzheimer's disease, ALS, Huntington's disease and Parkinson's disease, but in essence they addressed a simple, two-part question: What goes wrong in the aging brain and how can finding that out help us do something about it? Their answers provided many tangible signs of progress and reasons for hope.

More than 1,300 people from 48 countries tuned in online over the course of the day.

"Neurodegeneration is a very multifaceted and difficult problem that affects tens of millions of people around the world," said Li-Huei Tsai, Picower Professor of Neuroscience, director of The Picower Institute and founding director of the ABI. "The good news is that many very talented and dedicated researchers are working on it."

Speaker after speaker not only shared new insights into the nature of diseases that cause brain cells to die, but also described promising new treatment strategies. Some are advancing through clinical trials.

Keynote speaker Don Cleveland of the University of California at San Diego described a technology called antisense oligonucleotide therapy, which involves synthesizing "designer DNA drugs" that can intercede to compensate for a genetic mutation, either by reducing the production of harmful proteins or enhancing needed protein production. His lab helped to pioneer the idea for ALS in 2006 and now it's being applied to treat spinal muscular atrophy and is being tested for Huntington's disease and ALS.

Neurologist Diane Chan is leading human clinical studies in Tsai's lab of a potential Alzheimer's therapy. After observing that the power of neural rhythms at "gamma" frequency of 40 Hz are lessened in Alzheimer's, Tsai's lab led the discovery that exposing mice to light or sound at that frequency can increase gamma power and restore synchrony of neural activity across brain regions. In mouse models the technique improves memory and cognition, prevents neural death and reduces the accumulation of proteins known as key biomarkers of disease progression. In a small sample of human volunteers tested so far, the method has proven safe and well tolerated, increases 40 Hz gamma rhythm power and network connectivity and may be contributing to improved sleep, Chan reported. Testing for improvements in memory and cognition have not been completed yet, however.

Dorothy Schafer of the University of Massachusetts Medical School and Marco Colonna of Washington University are both looking at brain immune cells called microglia. In a mouse model of multiple sclerosis, Schafer has pinpointed the molecular process by which microglia end up engulfing and destroying the connections between neurons, called synapses. Her team has shown that overexpression of a protein that specifically blocks that action preserves synapses and protects brain function.

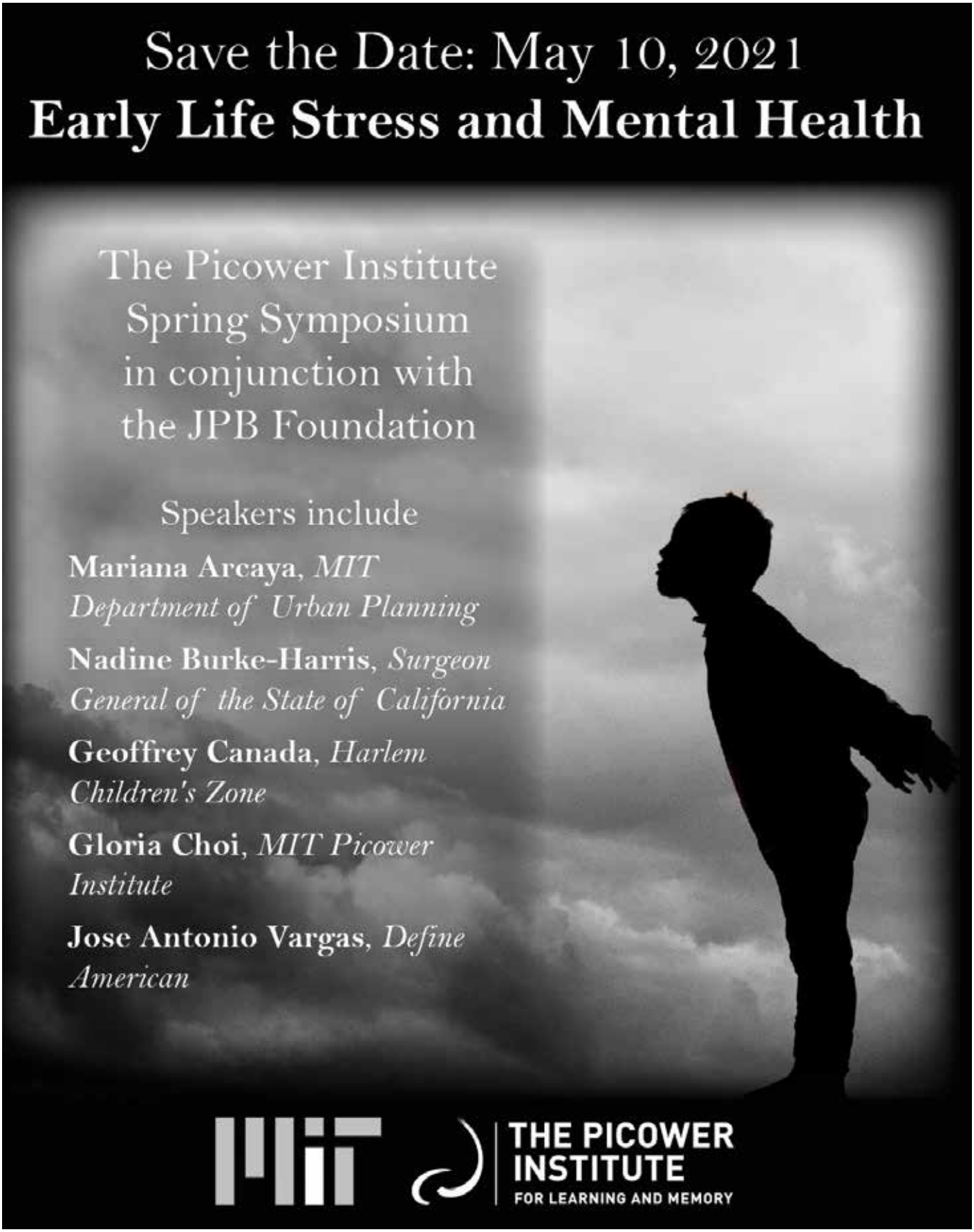
Colonna has shown that in people with particular variants of the gene *Trem2*, microglia fail to surround and engulf amyloid beta protein as they should but he has also found an antibody that stimulates microglia with these deficiencies to spring back into action.

Several speakers discussed the problem of protein misfolding and aggregation in neurodegeneration. Valina Dawson of Johns Hopkins University showed how toxic forms of a protein called alpha synuclein might invade the brain by traveling from the gut through the vagus nerve. That causes alpha synuclein already there to misfold, explaining how it can lead to Parkinson's disease damage. Dawson's lab has also identified the receptor that lets toxic alpha synuclein into neurons and has shown that blocking that receptor protects cells.

In her studies of Huntington's, Picower Institute member Myriam Heiman has sought to understand why specific cells in a region of the brain called the striatum are especially susceptible to an aggregation of huntingtin protein. To find out, she engaged in an unbiased genetic screen of the entire mouse genome, looking for genes that, if knocked out, would make neurons carrying the Huntington's mutation especially vulnerable. In her talk she described her recent study that found several genes including a novel one, *Nme1*. Further investigation revealed that *Nme1* likely helps promote clearance of huntingtin aggregates. In disease model mice, she showed that overexpressing *Nme1* reduced disease symptoms.

Another troublesome protein is tau. Lennart Mucke of the University of California at San Francisco presented evidence that in both Alzheimer's and even some autism spectrum disorders, tau can still enable dysfunction in disease processes, even when tau itself is in a healthy form. For instance, he's found that the protein is necessary for neuronal hyperexcitability to emerge in Alzheimer's disease models. His research suggests that lowering overall healthy tau levels might have therapeutic benefits in some diseases.

For extended coverage of the symposium visit **http://bit.ly/ABI-2020**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BOTTOM ROW: **Earl Miller**, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences; **Elly Nedivi**, William R. (1964) & Linda R. Young Professor of Neuroscience, The Picower Institute for Learning and Memory, Departments of Brain and Cognitive Sciences and Biology; **Mriganka Sur**, Paul E. Newton Professor of Neuroscience, Director of The Simons Center for the Social Brain; **Susumu Tonegawa**, Picower Professor of Biology and Neuroscience, Departments of Brain and Cognitive Sciences and Biology, Investigator, Howard Hughes Medical Institute, Investigator and Director of the RIKEN-MIT Center for Neural Circuit Genetics; **Li-Huei Tsai**, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Director, The Picower Institute for Learning and Memory; **Matthew Wilson**, Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology, Associate Director, The Picower Institute for Learning and Memory.

Choi photo by Justin Knight