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THE MODEL REMODELER

A primer on plasticity, the brain's amazing ability to constantly adapt to and learn from experience

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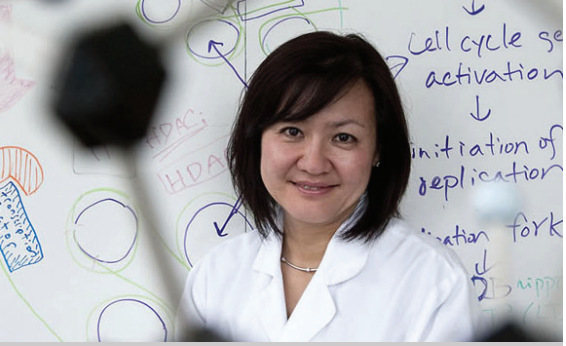
Neuroscience News

SPRING 2022

THE PICOWER INSTITUTE FOR LEARNING AND MEMORY

20 years OF DISCOVERY & IMPACT



DIRECTOR'S **MESSAGE**

Dear Friends,

We live in a complex world where anything can happen and there is always something new. It's no coincidence, but it's nonetheless very fortunate, that the brain has evolved to keep up with and even thrive throughout whatever each of our unique lifetimes will dish out. We are endowed with "plasticity," or the ability of the brain to adjust its physical configurations on numerous scales, and in numerous ways, to store, learn from, and adapt to our experiences.

Plasticity is so fundamental to learning and memory that many scientists here focus on discovering and understanding its many mechanisms. Because we therefore discuss the topic so often, we thought it would be helpful to dedicate our cover story (p. 8) just to explaining what it means and how it happens. It's a handy plasticity primer.

What makes the brain flexible and versatile, however, can also make it vulnerable. That's why in the course of studying mechanisms of plasticity, scientists here also have made important discoveries about brain disorders. That's one of the reasons why "basic" research is so valuable. By asking fundamental questions about how the brain works, we can gain insights that allow us to develop better clinical tools and therapies.

Our news stories this issue (pp. 2-6) span that fluid continuum between basic and clinical. We report findings about Down syndrome and autism informed by new mechanistic understandings. We also report on a fundamental circuit for integrating context into decisions and on how brain waves help us handle information. We also report on new tools for research and technologies to improve care of patients under anesthesia.

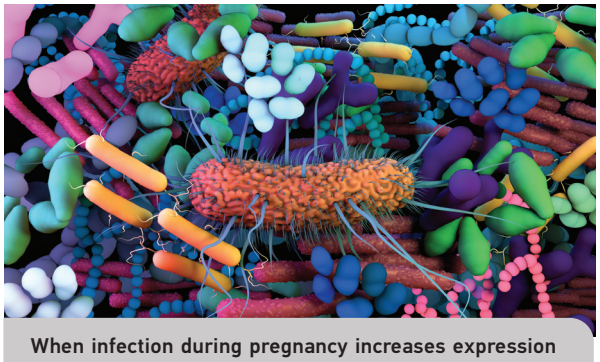
Our 20th Anniversary Exhibition May 10 will also feature short talks organized by the topics of learning and memory, plasticity and development, brain health and disease, and innovations and inventions. We hope you'll join us for this enlightening and celebratory event.

And If all this seems like a lot of new information, don't worry. You brain is equipped to handle it.

LI-HUEI TSAI, DIRECTOR

The Picower Institute for Learning and Memory

Research links **autism**, intestinal inflammation



When infection during pregnancy increases expression of the immune protein IL-17a, it changes the maternal microbiome, which can affect a newborn's immune system development.

MIT and Harvard Medical School researchers, working with mouse models, may have found an explanation for why many people with autism also experience intestinal inflammation when sick: When a mother experiences an infection during pregnancy and her immune system produces elevated levels of the molecule Interleukin-17a (IL-17a), that can not only alter brain development in her fetus, but also alter her microbiome such that after birth the newborn's immune system becomes primed for future inflammatory attacks.

Study co-senior authors Gloria Choi of MIT and Jun Huh of Harvard have traced how elevated IL-17a during pregnancy acts on neural receptors in a specific region of the fetal brain to alter circuit development, leading to autism-like behavioral symptoms.

"We've shown that IL-17a acting on the fetal brain can induce autism-like behavioral phenotypes such as social deficits," said Choi, Mark Hyman Jr. Career Development Associate Professor in The Picower Institute. "Now we are showing that the same IL-17a in mothers, through changes in the microbiome community, produces comorbid symptoms such as a primed immune system."

The new findings published in *Immunity* are yet to be confirmed in humans, but they suggest that central nervous and immune system problems in individuals with autism-spectrum disorders may share an environmental driver: maternal infection during pregnancy.

Eunha Kim and Donggi Paik of Huh's lab are the study's co-lead authors.

The team first confirmed that maternal immune activation (MIA) leads to intestinal inflammation in offspring by injecting pregnant mice with poly(I:C), a substance that mimics viral infection. Their offspring, but not the offspring of mothers in an unaffected control group, exhibited gut inflammation when exposed to other inflammatory stimuli.

To determine when the inflammatory problems are caused, the team switched mouse pups at birth so that ones born to MIA moms were reared by control moms and ones born to control moms were reared by MIA moms. The team found that pups born to MIA moms but reared by control moms exhibited the autism symptoms but not the intestinal inflammation. Pups born to control moms but reared by MIA moms did not show autism symptoms, but did experience intestinal inflammation. The results showed that while neurodevelopment is altered before birth, the immune response is altered postnatally.

The researchers found significant differences in diversity of the microbial communities in stool of MIA vs. control moms. To determine whether these differences played a causal role, they raised a new set of female mice in an environment where they do not carry any microbes in or on their body. Then the scientists transplanted stool from MIA or control moms into these "germ-free" mice and bred them with males. Only pups born to MIA-stool-transferred moms exhibited the intestinal inflammation.

Immune cells in pups from MIA moms showed gene transcription differences that promoted excessive secretion of IL-17a upon infection, explaining the inflammatory response.

The researchers hypothesized that the maternal microbiome is altered by the moms' IL-17a so they tested the effects of antibodies that block the cytokine. Blocking IL-17a in moms prior to immune activation prevented the intestinal inflammation in pups later in life.

In **Down syndrome** cells, genome-wide disruptions mimic a senescence-like state

In Down syndrome (DS), the third copy of chromosome 21 causes a reorganization of the 3D configuration of the entire genome in a key cell type of the developing brain, a new study shows. The resulting disruption of gene transcription and cell function are so similar to those seen in cellular aging, or senescence, that the scientists leading the study found they could use anti-senescence drugs to correct them in cell cultures.

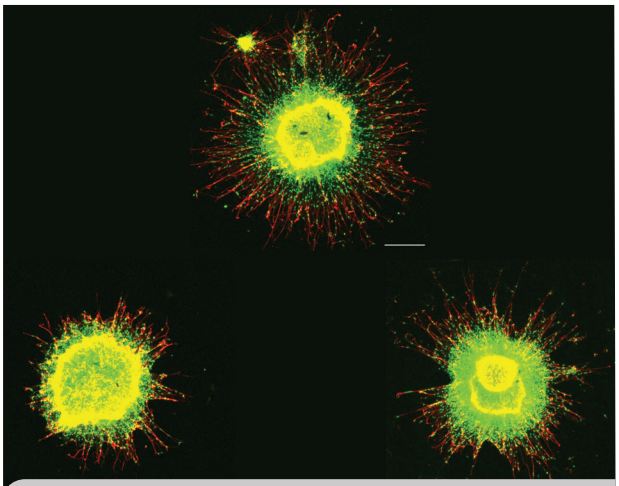
The study in *Cell Stem Cell* therefore establishes senescence as a potentially targetable mechanism for future treatment of DS, said Hiruy Meharena, a new assistant professor at the University of California San Diego who led the work as a Senior Alana Fellow in the Alana Down Syndrome Center at MIT.

"There is a cell-type specific genome-wide disruption that is independent of the gene dosage response," Meharena said. "It's a very similar phenomenon to what's observed in senescence. This suggests that excessive senescence in the developing brain induced by the third copy of chromosome 21 could be a key reason for the neurodevelopmental abnormalities seen in Down syndrome."

The study's finding that neural progenitor cells (NPCs), which develop into major cells in the brain including neurons, have a senescent character in DS is remarkable and novel, said senior author Li-Huei Tsai, but it is substantiated by the team's extensive work to elucidate the underlying mechanism of the effects of abnormal chromosome number, or aneupoloidy, within the nucleus of the cells.

"This study illustrates the importance of asking fundamental questions about the underlying mechanisms of neurological disorders," said Tsai, Picower Professor of Neuroscience and director of the Alana Center and of The Picower Institute. "We didn't begin this work expecting to see senescence as a translationally relevant feature of DS, but the data emerged from asking how the presence of an extra chromosome affects the architecture of all of a cell's chromosomes during development."

Meharena and co-authors measured distinctions in human cell cultures that differed only by whether they had a third copy of chromosome 21. Stem cells derived from volunteers were cultured to turn into NPCs. In both the stem cells and the NPCs, the team examined 3D chromosome architecture, several metrics of DNA structure and interaction, gene accessibility and transcription, and gene expression. They also looked at the consequences of the gene expression differences on important functions of these developmental cells, such as how well they proliferated and migrated in 3D brain tissue cultures. The NPCs were substantially affected by the third copy of chromosome 21.



Neural progenitor cells with the typical number of chromosomes show significant outward migration in culture (top). The bottom left culture shows untreated trisomy 21 cells. On the right are cells treated with anti-senescence drugs, which restored migration.

The presence of an extra copy causes all the other chromosomes to squish inward, like when people in a crowded elevator must narrow their stance to squeeze another person in. The main effects of this "chromosomal introversion," are more genetic interactions within each chromosome and less interactions among them. These changes and differences in DNA conformation within the cell nucleus lead to changes in how genes are transcribed and therefore expressed, causing important differences in cell function that affect brain development.

Meharena came to realize that these changes resembled the effects of senescence. The team decided to test whether anti-senescence drugs could undo the effects. They tested a combination of two: dasatinib and quercetin. The medications improved not only gene accessibility and transcription, but also the migration and proliferation of cells.

These drugs have strong side effects so they're not appropriate for intervention in DS, Meharena said. Instead an outcome of the study could be to prompt a search for medications that could have anti-senescence effects with a safer profile.

Senescence is a stress response of cells. Years of research by the late MIT biology professor Angelika Amon, who co-directed the Alana Center with Tsai, had shown that aneuploidy is a source of considerable stress for cells. A question raised by the new findings, therefore, is whether the senescence-like character of DS NPCs is indeed the result of an aneuploidy induced stress and if so, exactly what that stress is.

Another implication of the findings is how excessive senescence among brain cells might affect people with DS later in life. The risk of Alzheimer's disease is much higher at a substantially earlier age in the DS population than among people in general. In large part this is believed to be because a key Alzheimer's risk gene, APP, is on chromosome 21, but the newly identified inclination for senescence may also accelerate Alzheimer's development.

‘Traveling’ brain waves may help **working memory**

Brain waves spatially propagate, or “travel,” through brain regions over time. A new study by researchers at The Picower Institute measured how waves travel in the brain’s prefrontal cortex during working memory to investigate the functional advantages this apparent motion may produce.

A stadium wave forms when fans stand up and then sit back down in successive sections around the seating area. This creates a wave that travels through the crowd even though no individual fans move with it. A new study finds that working memory is accompanied by brain waves rotating around central points, analogous to this action.
Image by Ken Lund from Reno, Nevada, USA, CC BY-SA 2.0. via Wikimedia Commons.

“Most of the neuroscience literature involves lumping electrodes together and analyzing for time variations,” like changes in power at a particular frequency, said lead author Sayak Bhattacharya, a postdoctoral Picower Fellow in lab of senior author and Picower Professor Earl Miller. “It is important to appreciate that there are spatial subtleties, too. Brain oscillations move across the cortex in the form of traveling waves. These waves are similar to stadium waves where nothing actually moves, but sequential on-and-off of neighbors give it the appearance of a traveling wave.”

In other words, while the neurons under an eavesdropping electrode might burst with activity at a particular frequency, it’s also true that just before they perked up, neurons nearby in some direction had done so and very soon some other neurons on the opposite side will follow suit. Bhattacharya, Miller and their co-authors conducted the study published in *PLOS Computational Biology* to learn what that might mean for the vital brain function of working memory, where we must hold new information in mind to put it to use. It’s how we remember the directions to the bathroom we were just told, or today’s specials at the restaurant.

Bhattacharya combed over data recorded from animals as they played a working memory game. He analyzed whether their brain waves were traveling at each moment and how.

He found there were many distinct waves at various frequency bands washing back and forth across the electrodes in various directions. Careful calculations revealed that the waves were actually rotating in circle-like patterns around central anatomical points within the prefrontal cortex (again, like the wave in a football stadium rotates around the seating area, centered on the field of play). That’s notable because in other traveling wave studies usually the waves are planar, meaning they just move across from one place to another rather than going around as if on a race track.

Moreover, Miller said, the waves changed direction in particularly important ways. When the animals were idle, different directions of motion (e.g. clockwise vs. counterclockwise) were pretty much evenly mixed but at different times during the task, specific directions became significantly more prominent in various frequency bands. This was especially true among beta frequency waves, which became much more uniform in their direction only while the animals played the game. Other frequencies became more weighted toward particular directions during specific phases of the game. These changes suggested that the directions matter to how the brain organizes its responses to the task.

“The waves are generally traveling but the brain can change how the waves travel to suit different cognitive functions,” Miller said.

There are several ways that rotating traveling waves could aid working memory, he noted. A key requirement of working memory is being able to keep information at the forefront of conscious thought while it’s needed. A stationary wave (one in which all the neurons involved were “on” or “off” in unison) would mean that information could be unavailable when activity was off across the whole group. With a rotating traveling wave there is always activity somewhere around the circle – just like how in a stadium the next section stands up as soon as the preceding one sits down.

For another example, rotating waves could provide neurons with a regularly recurring stimulation with precise timing, Miller continued. That may promote strengthening connections within these coordinated groups via a phenomenon called spike-timing dependent plasticity in which the timing of input to a neuron influences how strongly it will connect with the partner that delivered the signal. The researchers also speculate that timing might also matter in another prefrontal cortex function: making predictions.

More work needs to be done to know with certainty how traveling waves aid working memory. Bhattacharya said new insight could come from investigating how they look when working memory doesn’t work.

“This working memory task was pretty easy and our animals did them without much error,” he said. “We want to study more complicated tasks—maybe multi-item working memory—and check if the traveling waves are disrupted somehow during the error trials. This would lead to interesting insight about the computational abilities of these waves.”

Feast or forage: Circuit helps a brain decide

MIT neuroscientists have discovered the elegant architecture of a fundamental decision-making brain circuit that allows a *C. elegans* worm to either forage for food or stop to feast when it finds a source. Capable of integrating multiple streams of sensory information, the circuit employs just a few neurons to sustain long-lasting behaviors, and yet flexibly switch between them as environmental conditions warrant.

"For a foraging worm, the decision to roam or to dwell is one that will strongly impact its survival." said Steven Flavell, Lister Brothers Career Development Associate Professor in The Picower Institute and senior author of the study in *eLife*. "We thought that studying how the brain controls this crucial decision-making process could uncover fundamental circuit elements that may be deployed in many animals' brains."

Though the critical component of brain circuitry may seem simple now that it has been revealed, finding it was anything but easy. Lead author Ni Ji, a postdoc in Flavell's lab, used several advanced technologies, including one of the lab's own invention, to figure it out.

C. elegans is a popular model in neuroscience because it only has 302 neurons and the "wiring diagram," or connectome, has been fully mapped. But even so, the very dense and overlapping interconnectedness among those neurons, plus their ability to signal each other via chemicals called neuromodulators, means that one can hardly just look at the connectome and discern how it switches between different states of behavior.

But Flavell's lab developed a new microscope capable of constantly imaging the activity of neurons across the worm's brain, as indicated by calcium-triggered flashes of light, even as it moves around freely. Ji used the scope to focus on 10 interconnected neurons involved in foraging, tracking their patterns of neural activity associated with roaming or dwelling behaviors.

Computational analysis of neural activity patterns revealed a quartet of neurons whose activity was specifically associated with roaming. Another key pattern was that the transition from roaming around to stopping to dwell always followed activation of a neuron called NSM. Flavell's lab previously showed that NSM can sense the presence of newly ingested food and emit a neuromodulator called serotonin to signal other neurons to slow the worm down to dwell in a nutritive area.

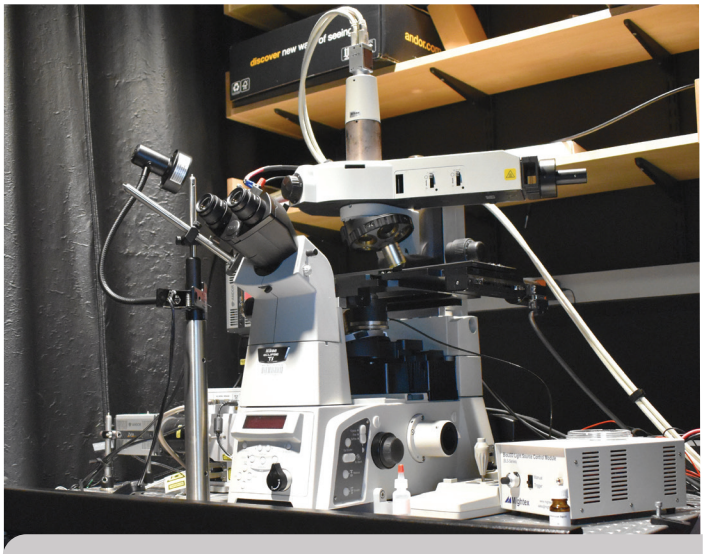
Having identified the activity patterns that changed as the worm switched states, Ji began manipulating neurons in the circuit to understand how they interact. To confirm NSM's role as the trigger of the dwelling state, Ji engineered it to be artificially activated with a flash of light (a technique called optogenetics). Doing so caused the worm to dwell by inhibiting the activity of the roaming-associated neurons. This inhibition depended on the roaming neurons having a serotonin receptor called MOD-1. If Ji genetically knocked out MOD-1, NSM couldn't inhibit the roaming behavior and quickly stopped trying for lack of feedback.

Similarly, Ji showed that when the worm was roaming, it was because the roaming quartet was using the neuromodulator PDF to inhibit the activity of NSM.

How does the worm decide to switch between roaming and dwelling? Ji and colleagues programmed a machine learning algorithm to discern which neurons might work upstream in the broader circuit to influence the serotonin and PDF tug of war. This approach identified a neuron called AIA, known for integrating sensory information about food odors. AIA's activity co-varied with a couple of the roaming neurons during roaming, and with NSM when dwelling began.

So upon becoming activated by the smell of food, AIA could use its input to drive either side of the mutual inhibitory circuit to switch behavior. Remembering that NSM can sense when the worm is actually eating, Ji and Flavell could deduce what AIA and NSM must be doing. If the worm smells food but is not eating, it needs to roam further to that food smell until it is. If the worm smells food and at the same time it begins eating, then it should continue to dwell there.

"To a foraging worm, food odors are an important, but ambiguous, sensory cue. AIA's ability to detect food odors and to transmit that information to these different downstream circuits, dependent on other incoming cues, allows animals to contextualize the smell and make adaptive foraging decisions," Flavell said. "If you are looking for circuit elements that could also be operating in bigger brains, this one stands out as a basic motif that might allow for context-dependent behaviors."



Using a new microscope system the Flavell lab invented, researchers could track changes in the activity of individual neurons as worms moved and behaved freely.

Tissue expansion improves neural imaging

When structures such as the proteins that build nerve cell connections are too small for a microscope to resolve, tissue expansion chemistry can make everything big enough to image. But sometimes chemical bonds form right where fluorescent antibody labels must attach to proteins to make them visible. Now Associate Professor Kwanghun Chung's lab has solved the problem, demonstrating vast improvements in imaging the structure of neural connections, or "synapses," with standard microscopes.

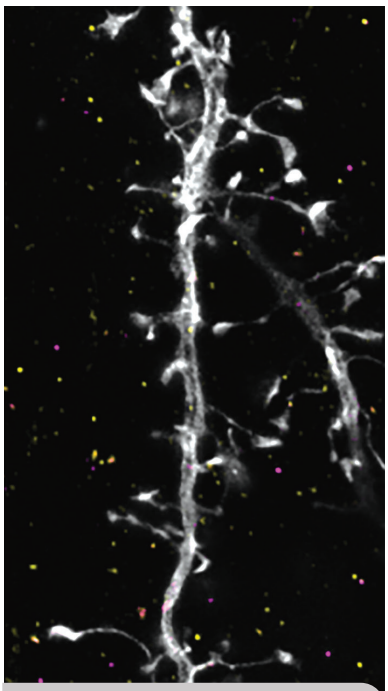
The new technology, "eMAP," upgrades the "magnified analysis of proteome," or MAP method Chung introduced in 2016. In *Science Advances*, Chung and lead authors Joha Park, Sarim Khan and Dae Hee Yun showed that with eMAP, many synapse proteins can now be imaged when they could not before.

Tissue expansion technologies work by infusing an acrylamide mesh into tissues to anchor all the proteins so that when the mesh is expanded, they all expand with it but stay in the same place relative to each other. The technologies typically accomplish that anchoring with chemical bonds of the fixative formaldehyde. The team's key advance with eMAP was reconfiguring the method to dispense with those chemical bonds in favor of weaving the mesh so finely, with more acrylamide, that proteins would just become physically entangled with it. That left binding sites on the proteins more accessible for fluorescent antibody labels.

In testing they found that among synaptic proteins, 49 out of 51 antibody labels could now attach with eMAP whereas only 35 could with MAP.

To explore the neuroscientific value of having these new labeling capabilities in expanded tissue, the team joined forces with MIT labs that study different mammalian synapses.

In one demonstration, the lab of Elly Nedivi, William R. (1964) & Linda R. Young Professor of Neuroscience, showed that by labeling components of receptors for the neurotransmitter GABA in inhibitory synapses (so called because they reduce a neuron's likelihood of producing an electrical signal), they could investigate whether the synapses' compositions ever differ. Indeed, they found that a little more than half of inhibitory synapses have both components they looked for, but a quarter had neither and some had only one or the other.



A section of neural dendrite imaged using eMAP. Colors indicate different inhibitory synapse proteins.

AI assistance for anesthesiologists advances

The day may be approaching when advanced artificial intelligence systems could assist anesthesiologists in the operating room.

In Artificial Intelligence in Medicine, MIT and Massachusetts General Hospital researchers revealed a deep reinforcement learning algorithm for continuously automating dosing of the anesthetic drug propofol. The algorithm outperformed more traditional software in sophisticated, physiology-based simulations of patients. It also closely matched the performance of real anesthesiologists when showing what it would do to maintain unconsciousness given recorded data from nine real surgeries.

The algorithm's advances increase the feasibility for computers to maintain patient unconsciousness with no more drug than is needed, thereby freeing up anesthesiologists for all the other responsibilities they have in the operating room, including making sure patients remain immobile, experience no pain, remain physiologically stable, and receive adequate oxygen, said co-lead authors Gabe Schamberg and Marcus Badgeley.

Senior author Emery N. Brown said the algorithm's potential to help optimize drug dosing could improve patient care.

"Algorithms such as this one allow anesthesiologists to maintain more careful, near continuous vigilance over the patient during general anesthesia," said Brown, Edward Hood Taplin Professor Computational Neuroscience and Health Sciences & Technology at MIT.

The research team endowed the software with two neural networks: an "actor" with the responsibility to decide how much drug to dose at every given moment, and a "critic" that helped the actor behave to maximize "rewards" specified by the programmer. The researchers experimented with three different reward systems: one that penalized only overdosing, one that questioned providing any dose, and one that imposed no penalties.

In every case they trained the algorithm with simulations of patients employing advanced models of how quickly propofol doses reach the relevant regions of the brain after doses are administered and how the drug actually alters consciousness there. Patient unconsciousness levels, meanwhile, were reflected in measures of brain waves.

The most effective reward system turned out to be the "dose penalty" one in which the critic questioned every dose the actor gave, constantly chiding the actor to keep dosing to a necessary minimum to maintain unconsciousness. They then tested that version on recorded surgery data.

Tsai earns honors for Alzheimer's research

Li-Huei Tsai receives the IBiS Distinguished Investigator 2021 from Santiago Romero-Brufau, an IBiS alumnus at Harvard University.

In December at a special symposium of the Seville Institute of Biomedicine in Spain, Picower Professor and Picower Institute Director **Li-Huei Tsai** received the IBiS 2021 Distinguished Investigator Award. The institute recognized her contributions related to the molecular and epigenetic mechanisms involved in learning, memory and Alzheimer's disease that have opened new perspectives of therapeutic intervention in neurodegeneration.

Santiago Romero-Brufau of Harvard University, an IBiS alumnus, came to MIT to deliver the award. Then Tsai delivered a keynote presentation on her research to the symposium audience via livestream. She described several findings her lab has made about the role different genes play in Alzheimer's disease risk by studying human cell cultures and postmortem brains.

Tsai also earned recognition in December from Expertscape, a company that methodically tracks publications to calculate whose work has been especially influential in different fields. Their sampling of the literature placed her among the top Alzheimer's researchers in the world.

Nedivi a finalist in MIT entrepreneurship competition

Elly Nedivi, William R. (1964) & Linda R. Young Professor of Neuroscience, is among nine faculty members chosen by the MIT Future Founders Initiative as a finalist for the MIT Future Founders Prize Competition. The initiative, established in 2020 to promote female entrepreneurship in biotech, will award a total of $450,000 to three winners to help commercialize their health-related inventions.

Despite increasing representation at MIT, female science and engineering faculty found biotech startups at a disproportionately low rate compared with their male colleagues, according to research led by the initiative's founders, MIT Professor Sangeeta Bhatia, MIT Professor and President Emerita Susan Hockfield, and MIT Amgen Professor of Biology Emerita Nancy Hopkins. In addition to highlighting systemic gender imbalances in the biotech pipeline, the initiative's founders emphasize that the dearth of female biotech entrepreneurs represents lost opportunities for society as a whole — a bottleneck in the proliferation of publicly accessible medical and technological innovation.

The Future Founders Initiative Prize Competition will be structured as a learning cohort in which participants will be supported in commercializing their existing inventions with instruction in market assessments, fundraising, and business capitalization, as well as other programming. The program, which is being run as a partnership between the MIT School of Engineering and the Martin Trust Center for MIT Entrepreneurship, provides hands-on opportunities to learn from industry leaders about their experiences, ranging from licensing technology to creating early startup companies. At the end of the program, the cohort members will pitch their ideas to a selection committee composed of MIT faculty, biotech founders, and venture capitalists. The grand prize winner will receive $250,000 in discretionary funds, and two runners-up will receive $100,000.

de Jesús-Cortés earns School of Science award

Congratulations to **Héctor de Jesús-Cortés**, a post-doc in the lab of Mark Bear, for earning an Infinite Expansion Award from the MIT School of Science. Six Brain and Cognitive Sciences faculty members joined in nominating him for his "awe-inspiring commitment of time and energy to research, outreach, education, mentorship, and community" including organizing programs to inspire and train budding scientists in Puerto Rico.

For instance, de Jesús-Cortés co-founded the Sagrado MIT Neuroscience Pre-College Program, which helps high school students all over Puerto Rico to gain more exposure to and knowledge about science careers. Of the 11 juniors who participated in 2020, many students were headed for colleges such as Stanford, Yale, Emory, Cornell and Georgia Tech. This past summer he also mentored two students in the MIT Summer Research Program in Biology and Brain and Cognitive Neuroscience, which provides undergraduates from non-research intensive and minority-serving institutions the opportunity to join the research programs of MIT labs.

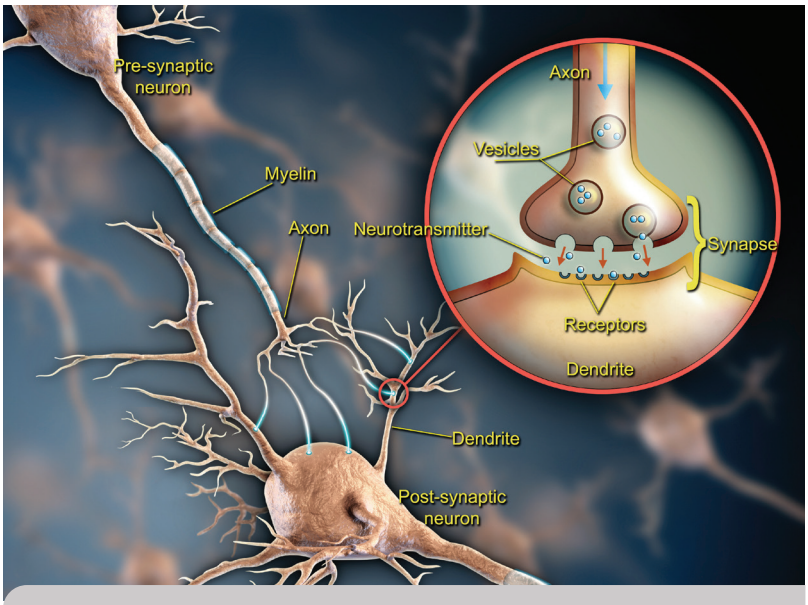
THE MODEL REMODELER

A Picower Institute primer on 'plasticity,' the brain's amazing ability to constantly adapt to and learn from experience

Muscles and bones strengthen with exercise and the immune system 'learns' from vaccines or infections, but none of those changes match the versatility and flexibility your central nervous system shows in adapting to the world. The brain is a model remodeler. If it weren't, you wouldn't have learned how to read this and you wouldn't remember it anyway.

The brain's ability to change its cells, their circuit connections, and even its broader architectures in response to experience and activity, for instance to learn new rules and store memories, is called "plasticity." The phenomenon explains how the brand-new brain of an infant can emerge from a womb and make increasingly refined sense of whatever arbitrary world it encounters – ranging from tuning its visual perception in the early months to getting an A in eighth-grade French. Plasticity becomes subtler during adulthood, but it never stops. It occurs via so many different mechanisms and at so many different scales and rates, it's… mind-bending.

Plasticity's indispensable role in allowing the brain to incorporate experience has made understanding exactly how it works – and what the mental health ramifications are when it doesn't – the inspiration and research focus of several Picower Institute professors (and hundreds of colleagues). *Neuroscience News* uses the term so often in its reports on both fundamental neuroscience and on disorders such as autism, it seemed high time these pages provided a primer. So here goes.



Plasticity playing field: When the brain changes to learn and adapt with experience, much (but not all) of the action occurs at connections neurons make called synapses.

Beginning in the 1980s and 1990s, advances in neuroanatomy, genetics, molecular biology and imaging made it possible to not only observe, but even experimentally manipulate mechanisms of how the brain changes at scales including the individual connections between neurons, called synapses; across groups of synapses on each neuron; and in whole neural circuits. The potential to discover tangible physical mechanisms of these changes proved irresistible to Picower Institute scientists such as Mark Bear, Troy Littleton, Elly Nedivi and Mriganka Sur.

Bear got hooked by experiments in which by temporarily covering one eye of a young animal, scientists could weaken the eye's connections to the brain just as their visual circuitry was still developing. Such "monocular deprivation" produced profound changes in brain anatomy and neuronal electrical activity as neurons rewired circuits to support the unobstructed eye rather than the one with weakened activity.

"There was this enormous effect of experience on the physiology of the brain and a very clear anatomical basis for that," Bear said. "It was pretty exhilarating."

Littleton became inspired during graduate and medical school by new ways to identify genes whose protein products formed the components of synapses. To understand how synapses work was to understand how neurons communicate and therefore how the brain functions.

"Once we were able to think about the proteins that are required to make the whole engine work, we could figure out how you might rev it up and down to encode changes in the way the system might be working to increase or decrease information flow as a function of behavioral change," Littleton said.

Built to rebuild

So what is the lay of the land for plasticity? Start with a neuron. Though there are thousands of types, a typical neuron will extend a vine-like axon to forge synapses on the root-like dendrites of other neurons. These dendrites may host thousands of synapses. Whenever neurons connect, they form circuits that can relay information across the brain via electrical and chemical signals. Most synapses are meant to increase the electrical excitement of the receiving neuron so that it will

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eventually pass a signal along, but other synapses modulate that process by inhibiting activity.

Hundreds of proteins are involved in building and operating every synapse, both on the "pre-synaptic" (axonal) side and the "post-synaptic" (dendritic) side of the connection. Some of these proteins contribute to the synapse's structure. Some on the pre-synaptic side coordinate the release of chemicals called neurotransmitters from blobs called vesicles, while some on the postsynaptic side form or manage the receptors that receive those messages. Neurotransmitters may compel the receiving neuron to take in more ions (hence building up electric charge), but synapses aren't just passive relay stations of current. They adjust in innumerable ways according to changing conditions, such as the amount of communication activity the host cells are experiencing. Across many synapses the pace and amount of neurotransmitter signaling can be frequently changed by either the presynaptic or postsynaptic side. And sometimes, especially early in life, synapses will appear or disappear altogether.

Moreover, plasticity doesn't just occur at the level of the single synapse. Combinations of synapses along a section of dendrite can all change in coordination so that the way a neuron works within a circuit is altered. These numerous dimensions of plasticity help to explain how the brain can quickly and efficiently accomplish the physical implementation of something as complex as learning and memory, Nedivi said.

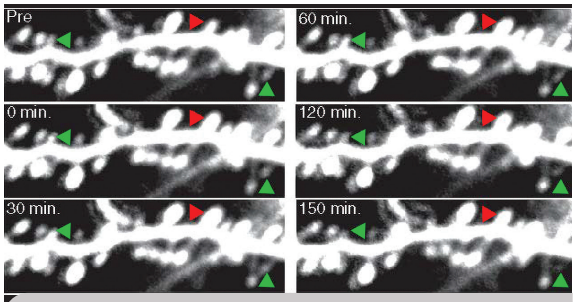
"You might think that when you learn something new it has nothing to do with individual synapses," Nedivi said. "But in fact, the way that things like this happen is that individual synapses can change in strength or can be added and removed, and then it also matters which synapses, and how many synapses, and how they are organized on the dendrites, and how those changes are integrated and summated on the cell. These parameters will alter the cell's response properties within its circuit and that affects how the circuit works and how it affects behavior."

A 2018 study in Sur's lab illustrated learning occurring at a neural circuit level. His lab trained mice on a task where they had to take a physical action based on a visual cue (e.g. drivers know that "green means go"). As mice played the game, the scientists monitored neural circuits in a region called the posterior parietal cortex where the brain converts vision into action. There, ensembles of neurons increased activity specifically in response to the "go" cue. When the researchers then changed the game's rules (i.e. "red means go") the circuits switched to only respond to the new go cue. Plasticity had occurred *en masse* to implement learning.

Many mechanisms

To carry out that rewiring, synapses can change in many ways. Littleton's studies of synaptic protein components have revealed many examples of how they make plasticity happen. Working in the instructive model of the fruit fly, his lab is constantly making new findings that illustrate how changes in protein composition can modulate synaptic strength.

For instance, in a 2020 study his lab showed that synaptotagmin 7 limits neurotransmitter release by regulating the speed with which the supply of neurotransmitter-carrying vesicles becomes replenished. By manipulating expression of the protein's gene, his lab was able to crank neurotransmitter release, and therefore synaptic strength, up or down like a radio volume dial.



Stronger and weaker: On a section of dendrite over a couple of hours Mriganka Sur's lab watched a dendritic spine housing a synapse grow (red arrows), while some of its neighbors shrank (green arrows).

Other recent studies revealed how proteins influence the diversity of neural plasticity. At the synapses flies use to control muscles, "phasic" neurons release quick, big bursts of the neurotransmitter glutamate, while tonic ones steadily release a low amount. In 2020 Littleton's lab showed that when phasic neurons are disrupted, tonic neurons will plasticly step up glutamate release, but phasic ones don't return the favor when tonic ones are hindered. Then last year, his team showed that a major difference between the two neurons was their levels of a protein called tomosyn, which turns out to restrict glutamate release. Tonic ones have a lot but phasic ones have very little. Tonic neurons therefore can vary their glutamate release by reducing tomosyn expression, while phasic neurons lack that flexibility.

Nedivi, too, looks at how neurons use their genes and the proteins they encode to implement plasticity. She tracks "structural plasticity" in the living mouse brain, where synapses don't just strengthen or weaken, but come and go completely. She's found that even in adult animal brains, inhibitory synapses will transiently appear or disappear to regulate the influence of more permanent excitatory synapses.

Nedivi has revealed how experience can make excitatory synapses permanent. After discovering that mice lacking a synaptic protein called CPG15 were slow learners, Nedivi hypothesized that it was because the protein helped cement circuit connections that implement learning. To test that, her lab exposed normal mice and others lacking CPG15 to stretches of time in the light, when they could gain visual experience, and the dark, where there was no visual experience. Using special microscopes to literally watch fledgling synapses come and go in response, they could compare protein levels in those synapses in normal mice and the ones without CPG15. They found that CPG15 helped experience make synapses stick around because upon exposure to increased activity, CPG15 recruited a structural protein called PSD95 to solidify the synapses. That explained why CPG15-lacking mice don't learn as well: they lack that mechanism for experience and activity to stabilize their circuit connections.

Another Sur Lab study in 2018 helped to show how multiple synapses sometimes change in concert to implement plasticity. Focusing on a visual cortex neuron whose job was to respond to locations within a mouse's field of view, his team purposely changed which location it preferred by manipulating "spike-timing dependent plasticity." Essentially right after they put a visual stimulus in a new location (rather than the neuron's preferred one), they artificially excited the neuron. The reinforcement of this specifically timed excitement strengthened the synapse that received input about the new location. After about 100 repetitions, the neuron changed its preference to the new location. Not only

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did the corresponding synapse strengthen, but also the researchers saw a compensatory weakening among neighboring synapses (orchestrated by a protein called Arc). In this way, the neuron learned a new role and shifted the strength of several synapses along a dendrite to ensure that new focus.

Lest one think that plasticity is all about synapses or even dendrites, Nedivi has helped to show that it isn't. For instance, her research has shown that amid monocular deprivation, inhibitory neurons go so far as to pare down their axons to enable circuit rewiring to occur. In 2020 her lab collaborated with Harvard scientists to show that to respond to changes in visual experience, some neurons will even adjust how well they insulate their axons with a fatty sheathing called myelin that promotes electrical conductance. The study added strong evidence that myelination also contributes to the brain's adaptation to changing experience.

It's not clear why the brain has evolved so many different ways to effect change (these examples are but a small sampling) but Nedivi points out a couple of advantages: robustness and versatility.

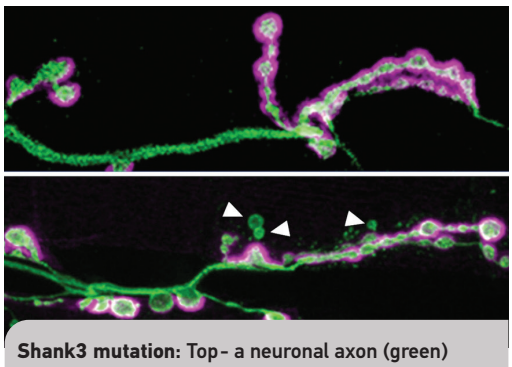
"Whenever you see what seems to you like redundancy it usually means it's a really important process. You can't afford to have just one way of doing it," she said. "Also having multiple ways of doing things gives you more precision and flexibility and the ability to work over multiple time scales, too."

Insights into illness

Another way to appreciate the importance of plasticity is to recognize its central role in neurodevelopmental diseases and conditions. Through their fundamental research into plasticity mechanisms, Bear, Littleton, Nedivi and Sur have all discovered how pivotal they are to breakdowns in brain health.

Beginning in the early 1990s, Bear led pioneering experiments showing that by multiple means, post-synaptic sensitivity could decline when receptors received only weak input, a plasticity called long-term depression (LTD). LTD explained how monocular deprivation weakens an occluded eye's connections to the brain. Unfortunately, this occurs naturally in millions of children with visual impairment, resulting in a developmental vision disorder called amblyopia. But Bear's research on plasticity, including mechanisms of LTD, has also revealed that plasticity itself is plastic (he calls that "metaplasticity"). That insight has allowed his lab to develop a potential new treatment in which by completely but temporarily suspending all input to the affected eye by anesthetizing the retina, the threshold for strengthening vs. weakening can be lowered such that when input resumes, it triggers a newly restorative connection.

Bear's investigations of a specific form of LTD have also led to key discoveries about Fragile X syndrome, a genetic cause of autism and intellectual disability. He found that LTD can occur when stimulation of metabotropic glutamate receptor 5 (mGluR5) causes proteins to be synthesized at the dendrite, reducing post-synaptic sensitivity. A protein called FMRP is supposed to be a brake on this synthesis but mutation of the FMR1 gene in Fragile X causes loss of FMRP. That can exaggerate LTD in the hippocampus, a brain region crucial for memory and cognition. The insight has allowed Bear to advance drugs to clinical trials that inhibit mGluR5 activity to compensate for FMRP loss.



Shank3 mutation: Top - a neuronal axon (green) forms many synapses, highlighted in purple. Bottom - an axon from a fruit fly lacking the Shank protein. Not as many synapses form, and some of them (indicated by the white arrows) do not fully mature.

Littleton, too, has produced insight into autism by studying the consequences of mutation in the gene Shank3, which encodes a protein that helps to build developing synapses on the post-synaptic side. In a 2016 paper his team reported multiple problems in synapses when Shank was knocked out in fruit flies. Receptors for a key form of molecular signaling from the presynaptic side called Wnt failed to be internalized by the postsynaptic cell, meaning they could not influence the transcription of genes that promote maturation of the synapse as they normally would. A consequence of disrupted synaptic maturation is that a developing brain would struggle to complete the connections needed to efficiently encode experience and that may explain some of the cognitive and behavioral outcomes in Shank-associated autism. To set the stage for potential drug development, Littleton's lab was able to demonstrate ways to bypass Wnt signaling that rescued synaptic development.

By studying plasticity proteins Sur's lab, too, has discovered a potential way to help people with Rett syndrome, a severe autism-like disorder. The disease is caused by mutations in the gene MECP2. Sur's lab showed that MECP2's contribution to synaptic maturation comes via a protein called IGF1 that is reduced among people with Rett. That insight allowed them to show that treating Rett-model mice with extra IGF1 peptide or IGF1 corrected many defects of MECP2 mutation. Both treatment forms have advanced to clinical trials. Late last year IGF1 peptide was shown to be effective in a comprehensive phase 3 trial for Rett syndrome and is progressing toward FDA approval as the first-ever mechanism-based treatment for a neurodevelopmental disorder, Sur said.

Nedivi's plasticity studies, meanwhile, have yielded new insights into bipolar disorder. During years of fundamental studies, Nedivi discovered CPG2, a protein expressed in response to neural activity that helps regulate the number of glutamate receptors at excitatory synapses. The gene encoding CPG2 was recently identified as a risk gene for bipolar disorder. In a 2019 study her lab found that people with bipolar disorder indeed had reduced levels of CPG2 because of variations in the SYNE1 gene. When they cloned these variants into rats, they found they reduced the ability of CPG2 to locate in the dendritic "spines" that house excitatory synapses or decreased the proper cycling of glutamate receptors within synapses.

The brain's ever-changing nature makes it both wonderful and perhaps vulnerable. Both to understand it and heal it, neuroscientists will eagerly continue studying its plasticity for a long time to come.

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