Early Life *Stress*

Spring symposium highlights sources of, responses to, pressures on mental health and barriers to opportunity. ***Pg. 8***

The 13 speakers and panelists at the Spring Symposium, "Early Life Stress and Mental Health"

Neuroscience News

MIT

SUMMER 2021

THE PICOWER INSTITUTE FOR LEARNING AND MEMORY

DIRECTOR'S **MESSAGE**

Dear Friends,

On May 10 we had the privilege of hosting an amazing slate of speakers at our Spring Symposium, "Early Life Stress and Mental Health," co-produced with the JPB Foundation. The diverse and fascinating talks challenged us to understand and address heart-rending problems such as adverse childhood experiences and systemic racism that can undermine lifelong health and deny people the chance to reach their full potential. Compelling and inspiring, the program blended science and stories to illuminate these issues and to present evidence and hope for solutions (see pg. 8).

Normally biennial, the symposium was delayed a year by the pandemic. Thankfully the pandemic has reached a moment where the evidence for hope is abundant, and we can reflect on its many lessons. At The Picower Institute, the success of moving our events online has shown us that technology allows people to learn from each other without always having to endanger our climate by flying to speak in person. Moreover, online lectures can reach larger and more diverse audiences all over the world. We have therefore pledged to reduce our air travel by at least 50 percent compared to pre-pandemic levels by continuing to move talks and meetings online (pg. 11). I'm also pleased that starting with this edition, this newsletter is now printing on 100 percent recycled paper.

There is more great news to relay. This spring two outstanding young members of our faculty, Myriam Heiman and Kwanghun Chung, earned tenure (pg. 7). We are overjoyed that their ingenious research and dedicated teaching have been so recognized.

In the following pages we recap exciting papers by Myriam's lab and many others. Read on to learn how a dietary supplement may reduce Alzheimer's risk, how brain circuits implement social distancing, and how anesthesia induces unconsciousness, an insight that can help improve patients' safety.

In a sometimes troubled world, research provides new evidence and hope.

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

Supplement may help counteract **Alzheimer's** risk gene

One of the most significant genetic risk factors for developing Alzheimer's disease (AD) is a gene variant called APOE4, which is carried by almost half of all AD patients. A new study shows that this gene has widespread effects on brain cells' ability to metabolize lipids and respond to stress.

MIT researchers found that APOE4 significantly disrupts brain cells' ability to carry out their normal functions. They also showed that treating these cells with extra choline, a widely available supplement safe for human use, could reverse many of these effects.

The researchers hope that their findings will lead to clinical studies of choline in people who carry APOE4, who make up about 14 percent of the overall population. Previous trials looking at choline's effects on cognition showed mixed results, but those trials were not targeted specifically to people with APOE4.

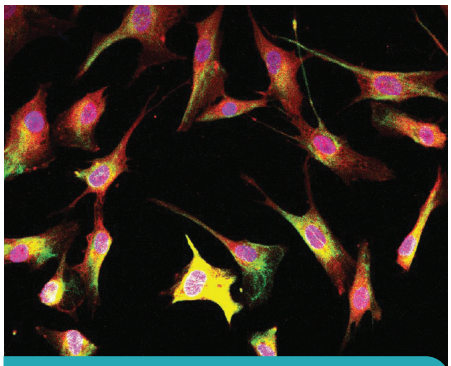
"What we would really like to see is whether in APOE4 carriers, if they take choline supplements to a sufficient amount, that would delay or give them some protection against developing dementia or AD," said Picower Professor Li-Huei Tsai, director of The Picower Institute.

Tsai and the late Susan Lindquist, former director of MIT's Whitehead Institute, are senior authors of the study in *Science Translational Medicine*. The paper's three lead authors are former Whitehead and MIT postdocs Grzegorz Sienski and Priyanka Narayan, and current MIT postdoc Julia Maeve Bonner.

The human APOE gene comes in three variants: APOE4 is linked to higher AD risk, APOE2 is considered protective, and APOE3, the most common variant, is neutral.

APOE is known to be involved in lipid metabolism, but its role in AD development has been unclear, Tsai says. To learn more, the researchers created human induced pluripotent stem cells with APOE3 or APOE4 but were otherwise identical genetically. They then stimulated these cells to differentiate into astrocytes, the brain cells that produce the most APOE protein.

APOE4 astrocytes showed dramatic changes in how they process lipids compared to APOE3. In APOE4 astrocytes, there was a significant buildup of neutral lipids and cholesterol. These astrocytes also accumulated droplets containing a type of lipids called triglycerides, and these triglycerides had many more unsaturated fatty acid chains than normal. These changes all disrupt the normal lipid balance inside the cells. The authors also noted APOE4-dependent lipid disruptions in another important brain cell, microglia.



Human astrocytes carrying the APOE4 Alzheimer's risk gene variant.

The researchers also found that yeast cells engineered to express the human version of APOE4 showed many of the same defects. But the researchers found that growing APOE4 yeast cells on a very nutrient-rich growth medium helped them to survive better than APOE4 yeast cells grown on the typical growth medium. Further experiments revealed that the nutrient that helped APOE4 cells survive is choline. The researchers then treated their human APOE4 astrocyte cells with choline and found that it also reversed much of the damage they had seen in those cells, including the accumulation of cholesterol and lipid droplets.

The researchers have now begun studying a mouse model of Alzheimer's that is also engineered to express the human APOE4 gene. They hope to investigate whether choline can help to reverse some of the symptoms of Alzheimer's in these mice.

"What our results suggest is that if you are an APOE2 or APOE3 carrier, even you are somewhat choline deficient you can cope with it," Tsai says. "But if you are an APOE4 carrier, then if you don't take enough choline, then that will have more dire consequences. The APOE4 carriers are more susceptible to choline deficiency."

Study finds circuit for distancing from sickness

When someone is sick, it's natural to want to stay as far from them as possible. It turns out this is also true for mice, according to an MIT study that also identified the brain circuit responsible for this distancing behavior.

In a *Nature* paper that explores how otherwise powerful instincts can be overridden in some situations, researchers from MIT's Picower Institute found that when male mice encountered a female mouse showing signs of illness, the males interacted very little with the females and made no attempts to mate with them as they normally would. The researchers also showed that this behavior is controlled by a circuit in the amygdala, which detects distinctive odors from sick animals and triggers a warning signal to stay away.

"As a community, it's very important for animals to be able to socially distance themselves from sick individuals," said Associate Professor Gloria Choi, the study's senior author. "Especially in species like mice, where mating is instinctively driven, it's imperative to be able to have a mechanism that can shut it down when the risk is high."

For mice and many other animals, certain behaviors such as mating and fighting are innately programmed, meaning that the animals automatically engage in them when certain stimuli are present. However, there is evidence that under certain circumstances, these behaviors can be overridden, Choi says.

"We wanted to see whether there's a brain mechanism that would be engaged when an animal encounters a sick member of the same species that would modulate these innate, automatic social behaviors," she says.

Previous studies have shown that mice can distinguish between healthy mice and mice that have been injected with a bacterial component called LPS, which induces mild inflammation when given at a low dose. These studies suggested that mice use odor, processed by their vomeronasal organ, to identify sick individuals.

To explore whether mice would change their innate behavior when exposed to sick animals, lead author Jeong-Tae Kwon, a postdoc, and co-authors placed male mice in the same cage with either a healthy female or a female that was showing LPS-induced signs of illness. They found that the males engaged much less with the sick females and made no effort to mount them.

The researchers then tried to identify the brain circuit underlying this behavior. The vomeronasal organ, which processes pheromones, feeds into a part of the amygdala called the COApm, and the team found that this region is activated by the presence of LPS-injected animals.

Further experiments revealed that activity in the COApm is necessary to suppress the males' mating behavior in the presence of sick females. When COApm activity was turned off, males would try to mate with sick females. Additionally, artificially stimulating the COApm suppressed mating behavior in males even when they were around healthy females.

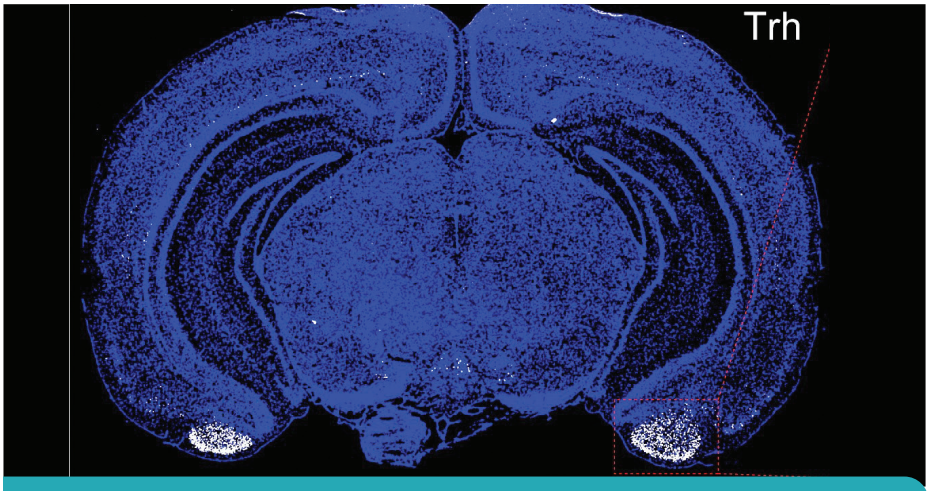
The researchers also showed that the COApm communicates with another part of the amygdala called the medial amygdala, and this communication, carried by a hormone called thyrotropin releasing hormone (TRH), is necessary to suppress mating behavior.

The link to TRH is intriguing, Choi says, because thyroid dysfunction has been implicated in depression and social withdrawal in humans. She now plans to explore the possibility that internal factors (such as mental state) can alter TRH levels in the COApm circuits to modulate social behavior.

"This is something we are trying to probe in the future: whether there's a link between thyroid dysfunction and modulation of this amygdala circuit that controls social behavior," she says.

This study is part of a larger effort in Choi's lab to study the role of neuro-immune interactions in coordinating "sickness behaviors." One area they are investigating, for example, is whether pathogens might attempt to exert control over the animals' behavior and stimulate them to socialize more, allowing viruses or bacteria to spread further.

"Pathogens may also have the ability to utilize immune systems, including cytokines and other molecules, to engage the same circuits in the opposite way, to promote more engagement," Choi says. "This is a sort of far-flung, but very interesting and exciting idea. We want to examine host-pathogen interactions at a network level to understand how the same neuro-immune mechanisms can be differently employed by the host versus pathogen to either contain or spread the infection, respectively, within a community. For example, we want to follow sick animals through their interactions within the community while controlling their immune status and manipulating their neural circuits."



White staining shows cells expressing thyrotropin releasing hormone (TRH) in the amygdala.

Anesthesia doesn't simply turn off the brain, it changes its rhythms

In a uniquely deep and detailed look at how the commonly used anesthetic propofol causes unconsciousness, a collaboration of Picower Institute labs shows that as the drug takes hold in the brain, a wide swath of regions become coordinated by very slow rhythms that maintain a commensurately languid pace of neural activity. Electrically stimulating a deeper region, the thalamus, restores synchrony of the brain's normal higher frequency rhythms and activity levels, waking the brain back up and restoring arousal.

"There's a folk psychology or tacit assumption that what anesthesia does is simply 'turn off' the brain," said Earl Miller, Picower Professor of Neuroscience and co-senior author of the study in *eLife*. "What we show is that propofol dramatically changes and controls the dynamics of the brain's rhythms."

Conscious functions, such as perception and cognition, depend on coordinated brain communication, in particular between the thalamus and the brain's surface regions, or cortex, in a variety of frequency bands ranging from 4 to 100 Hz. Propofol, the study shows, seems to bring coordination among the thalamus and cortical regions down to frequencies around just 1 Hz.

Miller's lab, led by postdoc Andre Bastos and former graduate student Jacob Donoghue, collaborated with that of co-senior author Emery N. Brown, who is Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience and an anesthesiologist at Massachusetts General Hospital. The collaboration therefore powerfully unified the Miller lab's expertise on how neural rhythms coordinate the cortex to produce conscious brain function with the Brown lab's expertise in the neuroscience of anesthesia and statistical analysis of neural signals.

Brown said studies that show how anesthetics change brain rhythms can directly improve patient safety because these rhythms are readily visible on the EEG in the operating room. The study's main finding of a signature of very slow rhythms across the cortex offers a model for directly measuring when subjects have entered unconsciousness after propofol administration, how deeply they are being maintained in that state, and how quickly they may wake up once propofol dosing ends.

"Anesthesiologists can use this as a way to better take care of patients," Brown said.

Algorithms accurately gauge unconsciousness under general anesthesia

Anesthestic drugs act on the brain but most anesthesiologists rely on heart rate, respiratory rate, and movement to infer whether surgery patients remain unconscious to the desired degree. In a new study, a research team based at The Picower Institute and Massachusetts General Hospital shows that artificial intelligence, attuned to the kind of anesthetic being used, can yield algorithms that assess unconsciousness in patients based on brain activity with high accuracy and reliability.

The algorithms offer the potential to allow anesthesiologists to maintain unconsciousness at the desired level while using less drug than they might administer when depending on less direct, accurate and reliable indicators, said senior author Emery N. Brown, Edward Hood Taplin Professor at MIT and an anesthesiologist at MGH. That can improve patient's post-operative outcomes, such as delirium.

"We may always have to be a little bit 'overboard'," Brown said. "But can we do it with sufficient accuracy so that we are not dosing people more than is needed?"

To train their machine learning algorithms, postdocs John Abel and Marcus Badgeley who led the study published in *PLOS ONE*, employed EEG data recorded in 2013 from seven healthy volunteers in their 20s who underwent anesthesia with the commonly used drug propofol. As the dose was methodically raised using computer controlled delivery, the volunteers were asked to respond to a simple request until they couldn't anymore. Then when they were brought back to consciousness as the dose was later lessened, they became able to respond again.

The team trained three algorithms, which were based on different underlying statistical methods, on more than 33,000 two-second-long snippets of the EEG recordings. This way the algorithms could "learn" the difference between EEG readings associated with consciousness and unconsciousness under propofol. Then the researchers tested the algorithms in three ways: on data from three other volunteers in the study, on data from 27 real patients who underwent surgery with propofol anesthesia and with data from 17 patients who underwent surgery with sevoflurane, which acts in the brain similarly to propofol.

The ability to predict unconsciousness across different drugs with the same mechanism of action is key, the authors said. A flaw of current EEG-based systems for monitoring unconsciousness, they said, is that they don't distinguish among drug classes, even though they work in very different ways, producing distinct EEG patterns.

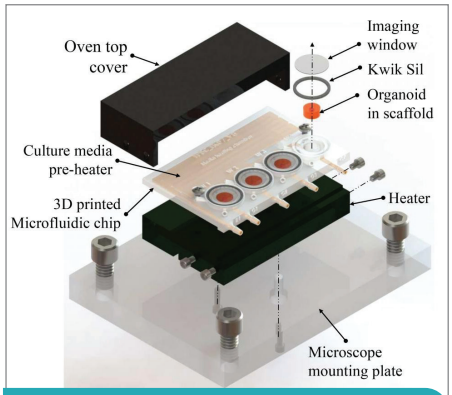
Tiny 'brains' grown in 3D-printed bioreactor

Scientists from The Picower Institute and the Indian Institute of Technology Madras have grown small amounts of self-organizing brain tissue, known as organoids, in a tiny 3D-printed system that allows observation while they grow and develop. The work is reported in *Biomicrofluidics*, by AIP Publishing.

Current technology for real-time observation of growing organoids involves the use of commercial culture dishes with many wells in a glass-bottomed plate placed under a microscope. The plates are costly and only compatible with specific microscopes. They do not allow for the flow or replenishment of nutrients to the growing tissue.

Recent advances have used a technique known as microfluidics, where nutrients are delivered through small tubes connected to a tiny platform or chip. These microfluidic devices are, however, expensive and challenging to manufacture.

The new invention uses 3D printing to create a reusable and easily adjustable platform that costs only about $5 per unit to fabricate. The design includes imaging wells for the growing organoids, microfluidic channels to provide nutrients, and preheating that supports tissue growth.



A 3D-printed microfluidic bioreactor for organ-on-chip cell culture. Image credit: Ikram Khan

By efficiently growing and sustaining organoids, neuroscientists can develop powerful models of brain development, both with healthy and disease-causing genetic backgrounds, said co-author Mriganka Sur, Newton Professor in The Picower Institute.

"The 3D printed bioreactor is an exciting new way to grow brain organoids long-term and observe their dynamics during normal and abnormal development," Sur said. "Combined with our lab's innovative technologies for imaging organoids noninvasively *in situ*, this provides a new way to observe the dynamics of cortical development in organoids, and how they go awry in disorders of brain development."

Indeed, co-first author Chloé Delepine, a postdoc in the Sur Lab, is actively using the reactors for live imaging of organoids modeling Rett syndrome, a devastating neurodevelopmental disorder and the leading known genetic cause of autism in girls.

"Our design costs are significantly lower than traditional petri dish- or spin-bioreactor-based organoid culture products," said IIT Madras co-first author Ikram Khan, a former MIT visiting student. "In addition, the chip can be washed with distilled water, dried, and autoclaved and is, therefore, reusable."

Cell health wears down in **Huntington's**

Using an innovative computational approach, researchers at MIT and Sorbonne Université found that Huntington's disease may progress to advanced stages more because of a degradation of the cells' health maintenance systems than because of increased damage from the disease pathology itself.

The analysis published in *eLife* revealed a trove of specific gene networks governing molecular pathways that disease researchers could target to sustain brain cell health amid the devastating neurodegenerative disorder, said Myriam Heiman, Associate Professor and co-senior author.

In the study, the team created a process called "*Geomic*" to integrate two large sets of data from Heiman's lab and one more from UCLA. *Geomic* created plots of the data that mapped differences in expression pertaining to 4,300 genes along dimensions such as mouse age, the extent of Huntington's-causing mutation, and cell type (certain neurons and astrocytes in a region of the brain called the striatum are especially vulnerable in Huntington's). The plots took the form of geometric shapes, like crumpled pieces of paper, whose deformations could be computationally compared to identify genes whose expression changed most consequentially amid the disease.

The *Geomic* analysis highlighted a clear pattern. Over time, the cells' responses to the disease pathology—linked to toxic expansions in a protein called Huntingtin—largely continued intact, but certain highly vulnerable cells lost their ability to sustain gene expression needed for some basic systems that sustain cell health and function. These systems initially leapt into action to compensate for the disease but eventually lost steam.

"If we can maintain the expression of these compensatory mechanisms, it may be a more effective therapeutic strategy than just trying to affect one gene at a time," Heiman said.

One of the biggest breakdowns in an especially vulnerable cell type, Drd-1 expressing neurons, was maintaining the health of energy-producing components called mitochondria. Another was an especially dramatic decline in the neurons and in astrocytes of gene expression in pathways that govern endosome regulation, an essential process for determining where proteins go and when they are degraded within the cells.

Comparing the geometry of different data plots allows Geomic software to identify genes whose expression changed most consequentially amid Huntington's disease.

The researchers validated some of their top findings by looking at gene expression in post-mortem samples of brain tissue from human Huntington's patients.

Neural networks may need more than neurons

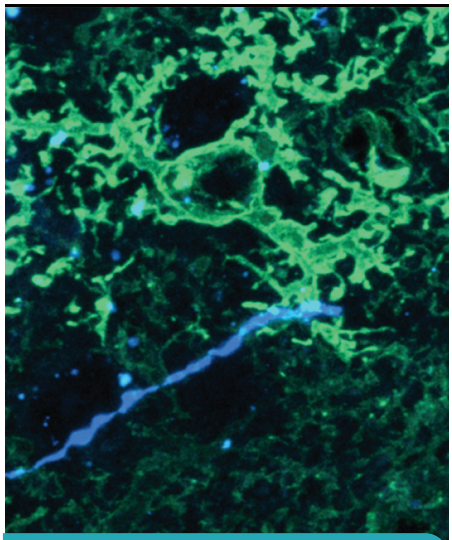
By encoding a feature of biological intelligence called reinforcement learning, in which we iteratively learn from successes and failures, "deep neural networks" (DNNs) have revolutionized artificial intelligence with spectacular demonstrations of mastery in Chess and Go. But they struggle to deal with the real-world problems encountered daily by humans and other animals. A new collaboration based at MIT posits that a fundamental shortcoming of deep neural networks is that they are *merely* neural. The team aims to prove DNNs could become much more powerful by integrating another brain cell type: astrocytes.

"Too much emphasis on neurons has removed any analysis of the role of these cells that are 50 percent of brain cells," said Mriganka Sur, Newton Professor of Neuroscience in The Picower Institute and leader of the project funded by the U.S. Army. The team includes four MIT faculty members as well as professors at California Institute of Technology and the University of Minnesota.

Today's state-of-the-art DNNs can remain woefully inefficient or outright oblivious to all kinds of factors that people and animals routinely must consider, Sur said. These include how to balance exploring an uncertain situation with exploiting it to advance toward the goal; how to keep track over time of which steps eventually prove crucial for success; and how to extract and transfer knowledge of those key steps for application in unexpected but related contexts.

There is growing evidence, Sur said, that astrocytes endow biological brains with these capabilities by acting as a parallel network overlaying that of neurons and helping to shape their circuit connections, or synapses.

"Our central hypothesis is that interaction of astrocytes with neurons and neuromodulators is a source of computational prowess that enables the brain to naturally perform reward learning and overcome many problems associated with state-of-the-art reinforcement learning (RL) systems," the team wrote in their grant. "Astrocytes can integrate and modulate neuronal signals across diverse timescales ranging from synaptic activity to shifts in behavioral state and learning. Our project is a combined effort of advancing the theory for RL systems and advancing the neurobiology of astrocytic function, through a synergistic design of theory and experiments."



An astrocyte (green) interacts with a neuron's axon (magenta). Image: Vincent Breton-Provencher.

Study of synapse strength focuses on 'active zones'

With a grant from the National Institutes of Health, the lab of Troy Littleton, Menicon Professor of Neuroscience in The Picower Institute, will seek to understand how neurons construct circuit connections called synapses of different strengths, a variety that may be key to the diversity of neural communication.

Littleton said the findings could increase scientists' understanding of how neural circuits develop and change to reflect learning and experience – a phenomenon called plasticity – and might also suggest ways to adjust synaptic strength when it is atypical in disorders such as autism or intellectual disability.

Using neurons that control muscles in the *Drosophila* fruit fly, the study will focus on "active zones" (AZs), which are tiny neural structures that enable the release of neurotransmitters across each synapse. The flies provide a simple model, Littleton said, that can help elucidate many basic factors affecting AZ strength that are also at play in the neurons of other animals, including mammals.

"Understanding the rules in a simple model like *Drosophila* that help to define when a synapse is strong or weak allows us to view these principles as fundamental elements of how neurons control synaptic growth and development," he said. "Depending on which of these factors a neuron modifies or plays around with, it is likely to be able to make synapses stronger or weaker in very different patterns."

In the new study, which will provide nearly $1.9 million over five years, the team will learn how AZs are built step by step out of more than a dozen different proteins that arrive at different stages of development. Because some AZs apparently build up bigger and stronger than others, Littleton likens the process to the construction of a variety of houses in a neighborhood—from big four-bedroom homes to little townhomes. The new study, including preliminary work the team has done with the support of the Picower Institute Innovation Fund, will help explain how each kind of structure emerges, in their relative abundance, in the same cell.

Li-Huei Tsai elected to American Academy of Arts & Sciences

Academy honors professor whose lab focuses on understanding and developing innovative treatment strategies for Alzheimer's

The American Academy of Arts & Sciences announced that Li-Huei Tsai, Picower Professor of Neuroscience and Director of The Picower Institute is among 252 luminaries elected to join its esteemed membership.

"We are honoring the excellence of these individuals, celebrating what they have achieved so far, and imagining what they will continue to accomplish," said David Oxtoby, President of the American Academy, in the announcement. "The past year has been replete with evidence of how things can get worse; this is an opportunity to illuminate the importance of art, ideas, knowledge, and leadership that can make a better world."

Tsai's laboratory focuses on advancing understanding of the molecular-, circuit- and systems-level mechanisms underlying neurodegenerative diseases such as Alzheimer's. She has translated many of her lab's fundamental insights into potential therapeutic approaches.

"I'm very honored to be elected to the academy and to be in the company of so many leading scholars and luminaries," Tsai said. "The Academy's mission of advancing the public good is also a philosophy that guides our work to understand and address neurodegenerative diseases such as Alzheimer's disease. This recognition encourages us to continue our efforts with urgency and rigor."

With her election, Tsai joins other Picower Institute faculty in the academy including Mark Bear, Emery N. Brown, Earl Miller, Mriganka Sur, Susumu Tonegawa and Matt Wilson. Also this year, four other MIT faculty members were elected to membership.

Greenough wins Infinite Mile recognition

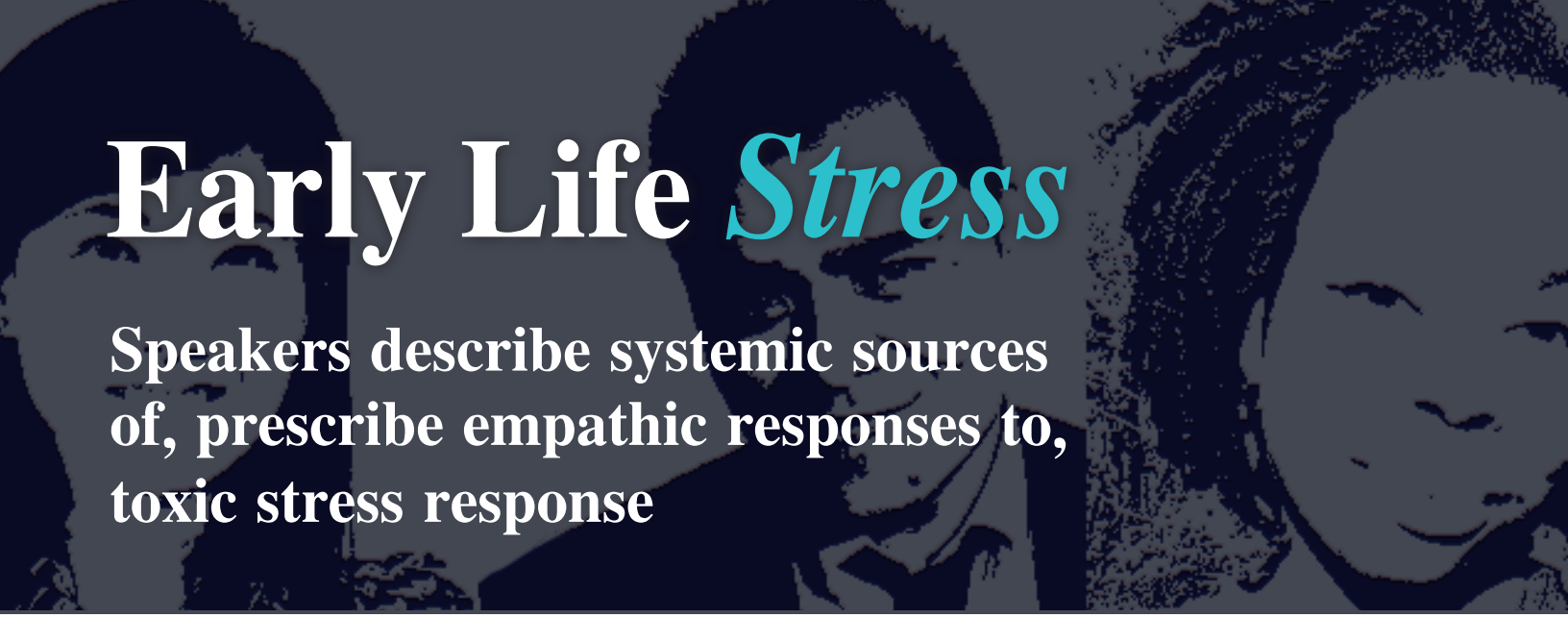
School of Science staff receive Infinite Mile Awards, presented annually since their creation in 2001, when their peers see that they have gone above and beyond in their roles and for making MIT a better place. Their support for the School of Science and MIT as a whole has been invaluable, especially after more than a year of operational disruption because of the Covid-19 pandemic.

Brittany Greenough, an events planning assistant in The Picower Institute headquarters, was nominated by Institute director and Picower professor of Brain and Cognitive Sciences Li-Huei Tsai and Administrative Officer William Lawson because, "in this new, virtual environment, Brittany has taken it upon herself to be the resident expert with transitioning events to online formats." With her help, Picower events went online, drawing record audiences from dozens of countries.

Chung, Heiman earn tenure

Congratulations to Associate Professors Myriam Heiman and Kwanghun Chung on earning tenure in the Departments of Brain and Cognitive Sciences and Chemical Engineering respectively!

Heiman's research includes an exploration of genetic dysregulation as a window on the vulnerability of certain cell types in neurodegenerative diseases such as Huntington's disease. Her work has revealed new potential therapeutic targets. Chung develops ingenious technologies that have enabled labs around the world to clarify, preserve, label, enlarge, image and ultimately analyze and understand tissue samples at multiple scales, including entire brains, and across multiple dimensions.



Early Life *Stress*

Speakers describe systemic sources of, prescribe empathic responses to, toxic stress response

At symposium, science and stories converge on harms of early exposure to trauma, racism but also restorative power of understanding, nurturing, and extending opportunity

A powerful series of speakers at the Picower Institute's biennial Spring Symposium, "Early Life Stress and Mental Health," blended personal stories and rigorous research to demonstrate that while remedying the lifelong toxic stress and disadvantage many people incur during childhood can be difficult, it is by no means intractable.

Picower Institute Director Li-Huei Tsai opened the symposium, co-produced with the JPB Foundation led by Barbara Picower, with the observation that while problems such as poverty, racism, injustice and child abuse have been around for a long time, finding and implementing ways to fight the health problems that can result has become increasingly urgent.

"This feels especially so right now as we grapple with a time in which many of us have seen young people endure historic stresses," she said. "The many tragedies and disruptions of the Covid-19 pandemic and stark examples of racial and social injustice have made this a particularly difficult time to grow up."

Stories of systemic stress

Educator Geoffrey Canada, founder and president of the Harlem Children's Zone, emphasized that the current moment is especially crucial in the black community.

"If I am right about what I suspect is going to happen in this country, I can just say for those of us who care about toxic stress we haven't seen nothing yet," he said. "What's coming in my opinion, is sort of unprecedented."

Canada, who grew up in the impoverished South Bronx, recounted several episodes in which generations of his family encountered racism, sometimes at the hands of police and health care providers. Many black people have come to regard such stresses as "the price of living in America," he said. But after observing the disproportionately terrible impacts of Covid-19 in his and other communities of color, his concern is heightened further.

"I think it's very clear in this country, your race determines largely whether you lived or died, whether you got sick, whether you ended up working at home or being on the front lines," he said, "whether your children got an education, and whether or not you're going to have anything that looks like a recovery from this experience."

Moreover, the murder of George Floyd and other police killings were "seared into the psyche," adding even more to the stresses black children now face.

Lawyer Bryan Stevenson, founder of the Equal Justice Initiative, called out other harms the justice system has inflicted, particularly on women and children. But he also recommended a prescription for the nation to reconsider policies that have led to mass incarceration and prosecution of children as adults.

"Over the last 25 years the percentage of women going to jails and prisons has increased 800%," he said. "Eighty percent of the women that we put in our jails and prisons are single parents with minor children which means that the lives of a generation of children are being disrupted by these carceral policies."

Moreover, in a country where 1 in 3 black and 1 in 6 Latino boys are projected to be in prison during their lives, Stevenson said that when he sits down with pre-teens in poor communities, "they'll say things that break my heart. I've talked to too many children who tell me that they expect to be in jail."

He called for more people to get "proximate" to families struggling with poverty, addiction, and other difficulties because proximity promotes understanding and empathy and provides an opportunity to provide the affirmation, care, safety and opportunity that children growing up among violence need. Proximity, for instance, can help undo the discredited but persistent narrative that

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juveniles accused of crimes are somehow "super predators" and not still children. It can combat the politics of fear and anger, he said, that led the country to treat addiction disorders through the legal system rather than as a health care problem. And it can dispel, he said, a sense in America, lingering since slavery and the genocide of Native Americans, of a racial hierarchy.

Jose Antonio Vargas put a similar emphasis on inspiring empathy through storytelling. The organization he founded, Define

Jose Antonio Vargas, founder of Define American.

American, is a culture change organization that uses the power of narrative to humanize conversations about immigrants. Vargas, who came to the U.S. from the Philippines as a child, discovered his undocumented status when he was a teenager. As difficult as living undocumented can be under typical circumstances—he drew a parallel between limitations on travel many felt during the Covid-19 pandemic with the restrictions undocumented people consistently face—becoming a public advocate amid intense policy debate can add to that stress.

Define American has therefore spearheaded research with the University of Massachusetts, Amherst, funded by the National Geographic Society, to survey immigration advocates for signs of PTSD, stress, depression, and other signs of mental health troubles, as well as resilience. Full results, he said, will be published this summer, but reflect high rates of both trauma and resilience.

Science begets solutions

Several symposium speakers emphasized that much as personal stories and proximity can reveal the roots of toxic stress, scientific data and research can also lead to remedies by discovering the mechanisms that underly health problems.

Picower Institute neuroscientist Gloria Choi, Associate Professor in the MIT Department of Brain and Cognitive Sciences (BCS), for example, shared her research tracing a long observed but never explained link between pregnant women getting sick from infection and the emergence of autism-like symptoms in their children. Her research in mouse models showed that when specific bacteria are in the gut microbiome of pregnant dams, infection during a specific time of pregnancy stimulates the release of cytokine molecules from immune cells. Those cytokines reach neurons in the S1DZ region of the cortex of the fetus, disrupting the development of inhibitory neurons. That in turn leads to hyperactivity of circuits governing social behaviors, causing the autism-like neurodevelopmental disorder.

By achieving this kind of detailed, causal understanding, Choi said, scientists poinpiont targets for therapeutic interventions.

"We scientists, to be able to help children, I think we need to understand at mechanistic levels how the mother's health can shape that of her child," she said.

At a population level, as well, extracting cause and effect from data can help guide public health and policy remedies, said social epidemiologist Mariana Arcaya, associate professor in MIT's Department of Urban Studies and Planning. She made the case that while many researchers have shown that neighborhood characteristics such as

Nadine Burke Harris, Surgeon General of the State of California.

poverty and violence can undermine health, fewer have studied what may be an equally important link – existing health conditions can make it harder for families to move. Appreciating this bidirectional relationship between health and geography should not be overlooked in devising interventions, she said. Her research has helped to document it.

"If poor health is a factor that is going to limit socioeconomic and geographic mobility, and we know that there's huge baseline disparities in health in the United States," Arcaya said, "then we really need to be concerned about the kind co-production of health and neighborhood and housing conditions and how some families may be in a kind of cyclical disadvantage for both health outcomes and socioeconomic and neighborhood outcomes."

As the first Surgeon General of the State of California, physician Nadine Burke Harris has galvanized a science-based statewide response to the public health crisis of adverse childhood experiences (ACEs), such as abuse, neglect or disruptions in home life. More than 60 percent of adults have experienced at least one ACE and 15.8 percent have experienced four or more. Research shows that ACEs accumulate to raise the risk of serious health problems including Alzheimer's disease and suicide. In all, ACE-related health problems, she said, add $112.5 billion to annual health care costs in California and more than $1 trillion across North America and Europe as a whole. On top of those, poverty and racism are also risk factors for future health difficulties.

"Over the last several decades we've begun to explore the biological mechanisms for how this happens," she said. "We've heard that trauma, especially in childhood, is damaging to our physical health, our mental health, but now we want to understand why because when we understand the mechanism, that gives us tools to be able to unpack this."

In affected people, she said, ACEs trigger toxic stress – an abnormally sustained stress hormone and immune system response, as well as epigenetic changes that alter expression of genes. These factors, many of which act directly on the brain, lead to health risks. They can be mitigated, however, by providing safe, stable, and nurturing relationships and environments, as well as with stress management and medication.

So California has launched programs that have trained more than 17,000 primary care providers to screen more than 300,000 patients for ACEs and toxic stress risk. From there doctors can help families with strategies to better manage the response. Moreover, the state has invested more than $30 million this year in grants covering 27 counties to link medical, social, educational and community service providers together in "trauma-informed networks of care" that support families more broadly.

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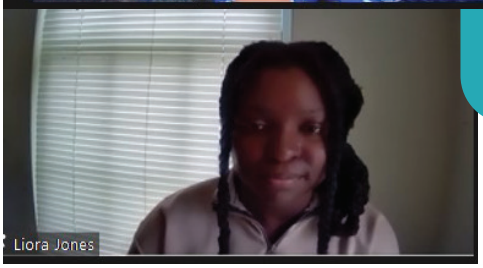


The Outreach and Opportunities in STEM panel (top row l. to r.): Laura Schulz, Eboney Hearn, Junyi Chu, (middle row) Kailande Cassamajor, Héctor de Jesús-Cortés, Tyler Bonnen and (bottom row) Liora Jones.

Early Life *Stress*

CONTINUED FROM PAGE 9

Extending opportunities

In a panel discussion, moderated by Laura Schulz, a Professor in BCS and the department's associate head for Diversity, Equity, Inclusion and Justice Initiatives, the symposium also highlighted another dimension of harmful inequity that prevents people from reaching their full potential: the lack of diversity in science, technology, engineering and mathematics, or "STEM." Mirroring the focus other speakers put on seeking solutions, the panel featured people at MIT who are working to improve diversity in STEM and participants in some of those programs who described what involvement has meant for them.

Picower Institute postdoc Héctor De Jesús Cortés, a member of Picower Professor Mark Bear's lab, for example, described how his participation as a student in Puerto Rico in the NIH-funded Minority Access for Research Careers program enabled him to do full time research and to launch his scientific career. That and other opportunities inspired him to co-found the Sagrado MIT Neuroscience Pre-College program, which helps high school students all over Puerto Rico to gain more exposure to science and knowledge about science careers. Of the 11 juniors who participated last year, many are now headed for colleges such as Stanford, Yale, Emory, Cornell and Georgia Tech, he said.

The MIT Office of Engineering Outreach Programs is currently serving about 365 high-achieving pre-college students from underrepresented groups and disadvantaged backgrounds. In all, OEOP has served more than 5,000 students, said Executive Director Eboney Hearn. About 80 percent have gone on to earn at least bachelor's degrees in STEM fields, she said, including many at MIT.

"Our alumni tell us that our programs have helped to level the playing field and helped them to get to places in their academic and personal journeys that didn't seem possible," she said.

Schulz's lab has been an active locus within BCS for inspiring and mentoring students at various stages. Graduate student Junyi Chu, for instance, described how last year she helped to launch the lab's high school internship program, in partnership with Somerville High School and Black Girls Code. The lab has already engaged 17 students in the lab's work studying cognition in babies. Interns also learn about science careers and publishing.

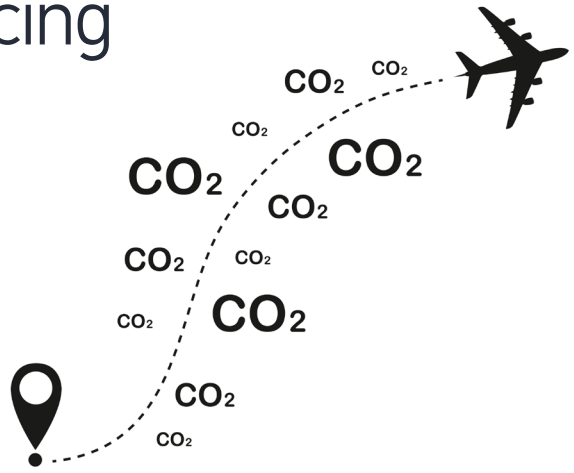
Panelist Liora Jones, from Torrington, CT, was a Schulz lab intern. She just graduated high school and will study cognitive science at Wellesley College in the fall. Inspired by the fields of human-computer interaction, psychology, and artificial intelligence, she said she saw the internship as a way to learn more about cognition and to gain research skills. She did, and in the process met a mentor, new friends, and attended her first research conference.

Chu has also mentored college students in the MIT Summer Research Program. Among them is Kailande Cassamajor, who just graduated from Howard University with a degree in biology and psychology, and will attend a master's program in data science at Columbia University in the fall. Cassamajor said she enjoyed the chance to meet fellow MSRP students from other schools as well as to work with graduate students, like Chu, who exposed her to cognitive and computational neuroscience. She greatly expanded her experience using a new programming language, for example.

In his remarks, panelist Tyler Bonnen provided a vivid, personal representation of many of the themes of the day. Now a fifth-year neuroscience graduate student at Stanford, he described his adolescence in Miami Dade County as "mired within the criminal justice system: rehabs, hospitals, jail cells, psych wards, detention centers." But he had a "good judge" and was lucky enough to be picked for a study in which he and his family were helped. He got out of the institutions in which he was being harmed, he said, did social justice work, and then found his way to community college, where he encountered a program that would finance his education if he would study science.

After earning a degree at Columbia, he studied at MIT as a BCS postbaccalaureate scholar with Schulz and Professor Rebecca Saxe. Now he's dedicating his multidisciplinary research to studying how memory works, with the goal of better understanding trauma and helping people overcome it. He's bringing his stories and science together to help others overcome acute stresses of their own.

Faculty commits to reducing post-pandemic air travel



Mindful of climate change and encouraged by the results of bringing scientific talks and conferences online during the Covid-19 pandemic, the faculty members of The Picower Institute for Learning and Memory at MIT have voted to slash the institute's future greenhouse gas (GHG) emissions from air travel at least in half.

The faculty resolution, approved May 5, creates a policy to encourage meeting the goal by limiting annual estimated GHG emissions to a mid-range cut off of 20 Metric Tons per lab per year. This is based on estimates of average, per-lab GHG emissions from two years prior to the Covid-19 pandemic (2018-2019). If any lab or the HQ exceeds the threshhold, it will face disincentives, for instance, incurring a $1,000 carbon "tax" paid within the institute.

"Our goal is for the whole institute to emit at least 50 percent less carbon from air travel than before the pandemic," said Picower Professor Earl K. Miller, the policy's chief architect. "Climate change is a global emergency. It is happening now. The time to act is now."

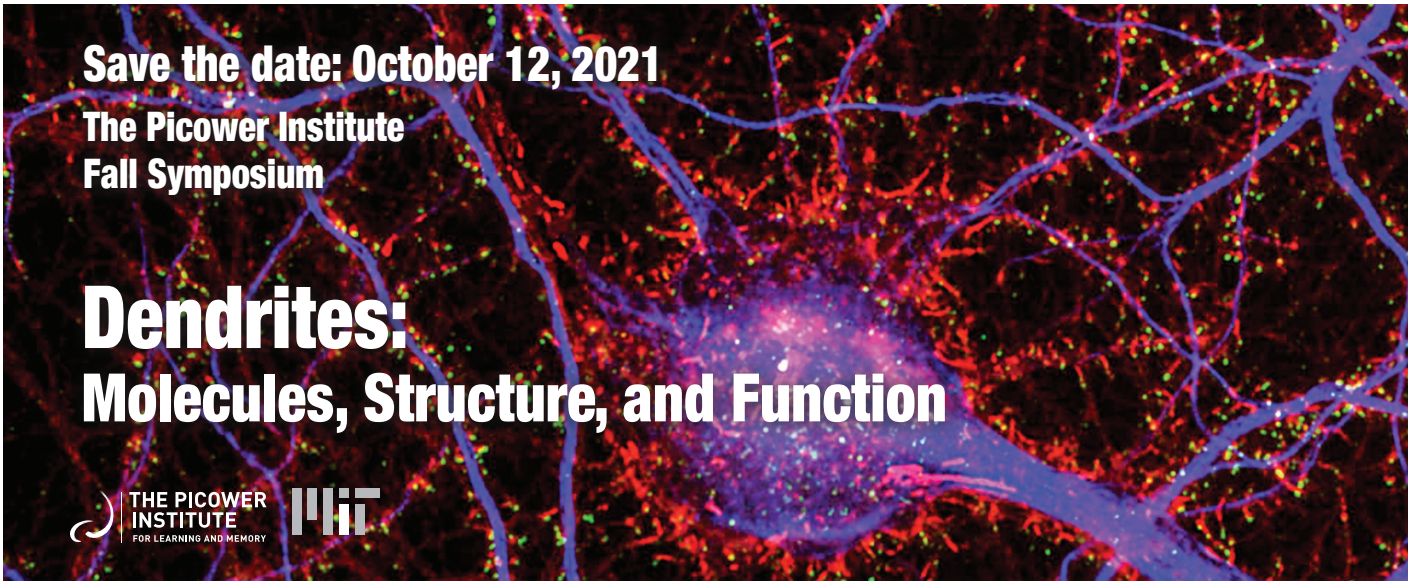
To meet the goal, faculty will seek to deliver more of their invited talks online and the Institute will fly in fewer speakers for its events, instead extending the offer for distant speakers to deliver their talks electronically. Institute public events such as symposia will be livestreamed, reducing the need for audience members to travel as well, though local attendees will be as welcome as ever.

"During the pandemic when we have brought all of our events online we have seen attendance surge, with people viewing our symposia from scores of countries around the world," said Institute Director and Picower Professor Li-Huei Tsai. "Acting to reduce our impact on climate can also make our scientific discussions more widely accessible."

As an additional step, the Institute will move more job interviews online, another practice that was required by the pandemic but can now remain in place because of its climate benefits.

To monitor the policy and to ensure transparency, Miller said, the Institute will publicly disclose its estimated GHGs on a new web page (https://picower.mit.edu/about/climate). Figures will be updated monthly. Estimates will be based on a method used by the MIT Office of Sustainability (MITOS), which estimates GHGs based on air travel expenditures.

"We embrace our responsibility to substantially reduce our numbers," Miller said. "We are always adopting innovative methods in our research. We should learn from the innovations made necessary during the pandemic to reduce our impact on the climate in the future."



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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