INSIDE

To the clinic!

When basic research yields discoveries with medical potential, Picower Institute professors find ways to test whether they'll help patients.

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Neuroscience News

MIT FALL 2022
THE PICOWER INSTITUTE FOR LEARNING AND MEMORY
20 years OF DISCOVERY & IMPACT

DIRECTOR'S **MESSAGE**

Dear Friends,

All this year as we've marked our 20th Anniversary, our theme has been "Discovery & Impact." Each of those ideas has many dimensions of meaning. Consider just one research paper: Typically it will contain many small discoveries that add up to a main one, the implications of that discovery (or even any of the little ones) could be numerous, and the study's many authors will have gained different degrees of additional experience and accomplishment that will advance their futures in the field.

In these endeavors, our focus is on fundamental research. Though each of our 13 labs study different things differently, we all seek to advance the field's foundational understanding of how the central nervous system works and how those mechanisms may falter amid disease. Invariably, when people study the brain at this "basic" level, they discover things of potential medical importance. For many of us, therefore, a clear and compelling dimension of our impact has turned out to be our ability to develop new therapeutic strategies with tangible clinical promise. When that happens, we work in different ways to ensure that the potential benefits are explored and realized. We present several examples of this dimension of our impact in our cover story (p. 9).

Speaking of research papers, you might notice that this edition is chock full of them. Our news section (p. 2-6) features summaries of eight new studies reporting fundamental advances in understanding Alzheimer's disease, Rett syndrome, the nature of neural communication, and neural and circuit activity underlying behavior.

All of these papers represent discoveries (two in particular also represent some marvelous imaging innovations). The full implications of each may not be known for years. But what we already can say with pride and confidence is that the students and postdocs who have led each paper have bright futures of decades of scientific contributions ahead of them.

We are grateful to have the chance to engage in these many dimensions of discovery and impact. Thank you for reading and for your support of our work.

LI-HUEI TSAI, DIRECTOR

The Picower Institute for Learning and Memory

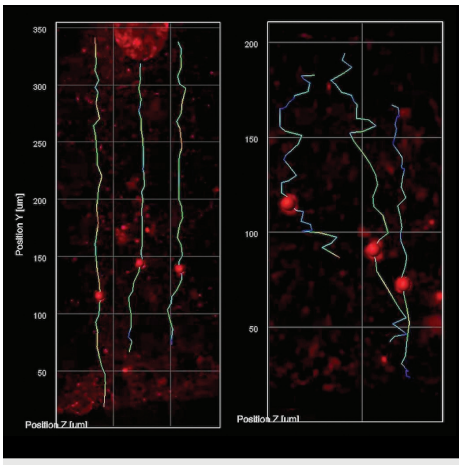
Neural migration becomes mired in **Rett syndrome**

Using an innovative microscopy method, Picower Institute scientists observed how newborn neurons struggle to reach their proper places in advanced human brain tissue models of Rett syndrome, producing new insight into how developmental deficits observed in the brains of patients with the devastating disorder may emerge.

Rett syndrome, characterized by symptoms including severe intellectual disability and impaired social behavior, is caused by mutations in the gene MECP2. To gain new insight into how the mutation affects the early stages of human brain development, researchers in the lab of Newton Professor Mriganka Sur grew 3D cell cultures called cerebral organoids, or "minibrains," using cells from people with MECP2 mutations and compared them to otherwise identical cultures without the mutations. Then the team led by postdoc Murat Yildirim examined the development of each type of minibrain using an advanced imaging technology called third harmonic generation (THG) three-photon microscopy.

THG, which Yildirim has helped to pioneer, allows for very high-resolution imaging deep into live, intact tissues without having to add any chemicals to label cells. The new study, published in *eLife*, is the first to use THG to image organoids, leaving them virtually undisturbed, Yildirim said.

"You should make sure you are not changing or affecting the neuronal physiology in any adverse way," Yildirim said.



In Rett syndrome organoids (right) neurons migrated erratically and more slowly than in neurotypical organoids (left).

The THG system allowed them to track the migration of newborn neurons as they made their way from the rim around open spaces in the minibrains (called ventricles) to the outer edge, which is directly analogous to the brain's cortex. They saw that the nascent neurons in the minibrains modeling Rett syndrome moved slowly and in meandering paths compared to the faster motion in straighter lines exhibited by the same cell types in minibrains without MECP2 mutation. Sur said the consequences of such migration deficits are consistent with what scientists, including in his lab, have hypothesized is going on in Rett syndrome fetuses.

"We know from postmortem brains and brain imaging methods that things go awry during brain development in Rett syndrome, but it has been astonishingly difficult to figure out what and why," said Sur, who directs the Simons Center for the Social Brain at MIT. "This method has enabled us to directly visualize a key contributor."

THG images tissues without labels because it is very sensitive to changes in the refractive index of materials, Yildirim said. It therefore resolves boundaries between biological structures, such as blood vessels, cell membranes and extracellular spaces. Because neural shapes change during their development, the team was able to also clearly see the delineation between the ventricular zone (the area around the ventricles where the newborn neurons emerge) and the cortical plate (an area that mature neurons settle into). It was also very easy to resolve various ventricles and segment them into distinct regions.

Those properties allowed the researchers to be able to see that in Rett syndrome organoids the ventricles were larger and more numerous and that the ventricular zones—the rims around the ventricles where neurons are born—were thinner. In live organoids they were able to track some of the neurons making their way toward the cortex over a few days—taking a new picture every 20 minutes—as neurons in real developing brains also attempt to do. They saw that Rett syndrome neurons achieved only about two thirds the speed of non-mutated neurons. The paths of the Rett neurons were also significantly more wiggly. The two differences combined meant that the Rett cells barely got half as far.

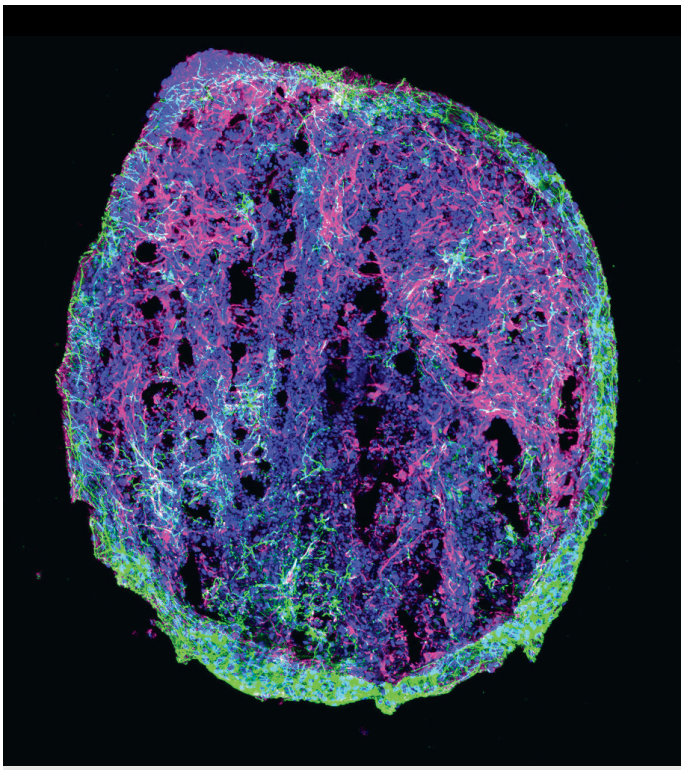
Microglia with APOE4 gene variant contribute to **Alzheimer's**

A hallmark of Alzheimer's disease is a reduction in the firing of some neurons in the brain, which contributes to the cognitive decline that patients experience. A Picower Institute study shows how a type of cells called microglia can contribute to this slowdown of neuron activity.

Microglia that express the APOE4 gene variant, one of the strongest genetic risk factors for Alzheimer's disease, cannot metabolize lipids normally. This leads to a buildup of excess lipids that interferes with nearby neurons' ability to communicate with each other. The findings suggest that if researchers could find a way to restore normal lipid metabolism in microglia, that might help to treat some of the symptoms of the disease.

Postdoc Matheus Victor is the lead author of the paper in *Cell Stem Cell.*

The APOE gene also comes in two other forms, known as APOE2, which is considered protective against Alzheimer's, and the most common form, APOE3, which is considered neutral. APOE3 and APOE4 differ by just one amino acid. About 14 percent of the population has the APOE4 variant, making it the most common genetic variant that has been linked to late-onset, nonfamilial Alzheimer's disease. People who carry one copy of APOE4 have a threefold higher risk of developing Alzheimer's, and people with two copies have a tenfold higher risk.



In this cultured spheroid neurons are stained purple among more general cell nuclei (blue) and astrocyte cells (green).

"If you look at the entire Alzheimer's disease population, about 50 percent of them are APOE4 carriers. So, it's a very significant risk, but we haven't known why this APOE4 allele presents such a risk," said Picower Professor and study senior author Li-Huei Tsai.

For several years, Tsai's lab has been studying the effects of APOE4 on a variety of cell types in the brain. To do this, the researchers use induced pluripotent stem cells, derived from human donors, and engineer them to express a specific version of the APOE gene.

These cells can then be stimulated to differentiate into brain cells, including neurons, microglia, and astrocytes.

A 2021 study by the lab showed that APOE4 astrocytes have dramatic impairments in their ability to process a variety of lipids, which leads to a buildup of molecules such as triglycerides, as well as cholesterol. In that paper, the researchers also showed that treating astrocytes expressing APOE4 with choline, a dietary supplement, could reverse many of the detrimental effects of APOE4.

In their new study, the researchers wanted to investigate how APOE4 affects interactions between microglia and neurons. Recent research has shown that microglia play an important role in modulating neuronal activity, including their ability to communicate within neural ensembles. Microglia also scavenge the brain looking for signs of damage or pathogens, and clear out debris.

The researchers found that APOE4 disrupts microglia's ability to metabolize lipids and prevents them from removing lipids from their environment. This leads to a buildup of fatty molecules, especially cholesterol, in the environment. These fatty molecules bind to a specific type of potassium channel embedded in neuron cell membranes, which suppresses neuron firing.

"We know that in late stages of Alzheimer's disease, there is reduced neuron excitability, so we may be mimicking that with this model," Victor said.

The buildup of lipids in microglia can also lead to inflammation, the researchers found, and this type of inflammation is believed to contribute to the progression of Alzheimer's disease.

The researchers also showed that they could reverse the effects of lipid overload by treating APOE4 microglia with a drug called Triacsin C, which interferes with the formation of lipid droplets. When APOE4 microglia were exposed to this drug, the researchers found that normal communication between neighboring neurons and microglia was restored.

"We can rescue the suppression of neuronal activity by APOE4 microglia, presumably through lipid homeostasis being restored, where now fatty acids are not accumulating extracellularly," Victor said.

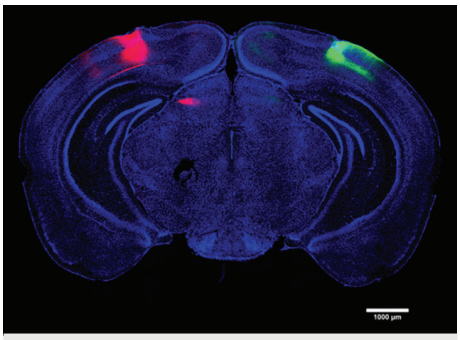
Triacsin C can be toxic to cells, so it would likely not be suitable to use as a drug to treat Alzheimer's, but the researchers hope that other approaches to restore lipid homeostasis could help combat the disease. In Tsai's 2021 APOE4 study, she showed that choline also helps to restore normal microglia activity.

"Lipid homeostasis is actually critical for a number of cell types across the Alzheimer's disease brain, so it's not singularly a microglia problem," Victor said. "The question is, how do you restore lipid homeostasis across multiple cell types? It's not an easy task, but we're tackling that through choline, for example."

When **Alzheimer's** degrades cells that cross hemispheres, visual memory suffers

A new MIT study finds that Alzheimer's disease disrupts at least one form of visual memory by degrading a newly identified circuit that connects the vision processing centers of each brain hemisphere.

The results of the study in *Neuron* come from experiments in mice, but provide a physiological and mechanistic basis for prior observations in human patients: the degree of diminished brain rhythm synchrony between counterpart regions in each hemisphere correlates with the clinical severity of dementia.



Scientists traced and studied neurons that connect the visual cortices in each hemisphere of the brain.

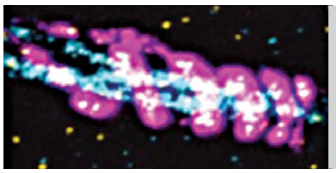
"We demonstrate that there is a functional circuit that can explain this phenomenon," said lead author Chinnakkaruppan Adaikkan, a former MIT postdoc who is now an assistant professor in the Centre for Brain Research at the Indian Institute of Science (IISc) in Bangalore. "In a way we uncovered a fundamental biology that was not known before."

Specifically, Adaikkan's work with senior author and Picower Professor Li-Huei Tsai identified neurons that connect the primary visual cortex (V1) of each hemisphere and showed that when the cells are disrupted, either by genetic alterations that model Alzheimer's disease or by direct laboratory perturbations, brain rhythm synchrony becomes reduced and mice become significantly less able to notice when a new pattern appears on a wall in their enclosures. Such recognition of novelty, which requires visual memory of what was there the prior day, is an ability commonly disrupted in Alzheimer's.

"This study demonstrates the propagation of gamma rhythm synchrony across the brain hemispheres via the cross hemispheric connectivity," Tsai said. "It also demonstrates that the disruption of this circuit in AD mouse models is associated with specific behavioral deficits."

The team discovered and traced V1 neurons that extended their axons all the way through the corpus callosum, which connects the brain's hemispheres, to cells in the V1 on the brain's other side. There, they found, the cross-hemispheric (CH) neurons forged connections, or synapses, with target cells, providing them with stimulation to drive their activity. Adaikkan also found that CH neurons were much more likely to be activated by a novelty discrimination task than V1 neurons in general. Then they examined how these cells differ amid Alzheimer's disease, identifying key deficits.

Microscopy technique reveals hidden structures



The newly seen helical structure of amyloid beta

Inside a living cell, proteins and other molecules are often tightly packed together. These dense clusters can be difficult to image because the fluorescent labels used to make them visible can't wedge themselves in between the molecules.

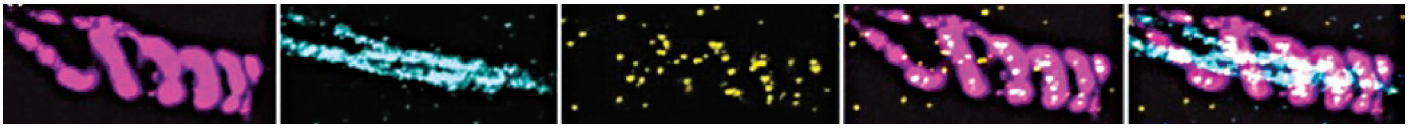
MIT researchers have now developed a novel way to overcome this limitation and make those "invisible" molecules visible. Their technique, described in *Nature Biomedical Engineering*, allows them to "de-crowd" the molecules by expanding a cell or tissue sample before labeling the molecules, which makes the molecules more accessible to fluorescent tags. This method builds on a widely used technique known as expansion microscopy previously developed at MIT.

"It's becoming clear that the expansion process will reveal many new biological discoveries. If biologists and clinicians have been studying a protein in the brain or another biological specimen, and they're labeling it the regular way, they might be missing entire categories of phenomena," says Edward Boyden, the Y. Eva Tan Professor in Neurotechnology and an affiliate member of The Picower Institute.

Using this technique, Boyden and colleagues including co-senior author and Picower Professor Li-Huei Tsai showed that they could image structures of key importance in neuroscience.

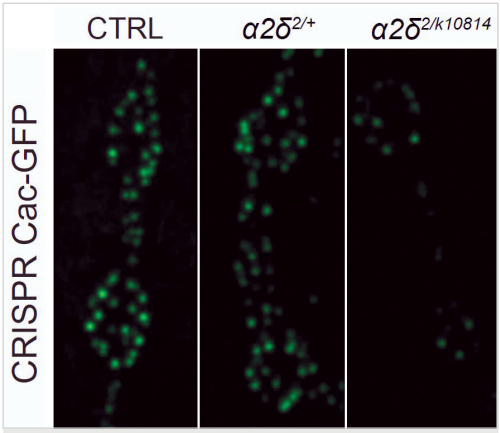
The researchers were able to identify tiny cellular structures within synapses, the connections between neurons that are densely packed with proteins. They labeled and imaged seven different synaptic proteins, which allowed them to visualize, in detail, "nanocolumns" consisting of calcium channels aligned with other synaptic proteins.

The researchers also used their new technique to image amyloid beta, a peptide that forms plaques in the brains of Alzheimer's patients. Using brain tissue from mice, the researchers found that amyloid beta forms periodic nanoclusters, which had not been seen before. These clusters of amyloid beta also include potassium channels. The researchers also found amyloid beta molecules that formed helical structures along axons. Boyden and his group members are now working with other labs to study cellular structures such as protein aggregates linked to Parkinson's and other diseases.



Neurons build **communication** capacity

The nervous system works because neurons communicate across connections called synapses. They "talk" when calcium ions flow through channels into "active zones" that are loaded with vesicles carrying molecular messages. The electrically charged calcium causes vesicles to "fuse" to the outer membrane of presynaptic neurons, releasing their communicative chemical cargo to the postsynaptic cell. In a new study, Picower Institute scientists provide several revelations about how neurons set up and sustain this vital infrastructure.



The more scientists knocked out a protein called alpha2delta with different manipulations (right two columns), the less Cac calcium channel accrued in synaptic active zones (green dots).

"Calcium channels are the major determinant of calcium influx, which then triggers vesicle fusion, so it is a critical component of the engine on the presynaptic side that converts electrical signals to chemical synaptic transmission," said Troy Littleton, senior author of the new study in *eLife* and Menicon Professor of Neuroscience. "How they accumulate at active zones was really unclear. Our study reveals clues into how active zones accumulate and regulate the abundance of calcium channels."

Neuroscientists have wanted these clues. One reason is that understanding this process can help reveal how neurons change how they communicate, an ability called "plasticity" that underlies learning and memory and other important brain functions. Another is that drugs such as gabapentin, which treats conditions as diverse as epilepsy, anxiety and nerve pain, binds a protein called alpha2delta that is closely associated with calcium channels. By revealing more about alpha2delta's exact function, the study better explains what those treatments affect.

Postdoc Karen Cunningham led the study. Using fruit fly motor neurons, she employed a wide variety of techniques and experiments to show for the first time the step by step process that accounts for the distribution and upkeep of calcium channels (Cac) at active zones.

At each active zone neurons seem to enforce a consistent cap on the amount of Cac present. When Cunningham genetically manipulated alpha2delta levels, she found that they directly determined how much Cac accumulated at active zones. Further experiments showed that alpha2delta constantly resupplies Cac to maintain the proper level. Larger active zones accrued more Cac than smaller ones. And in flies with mutated alpha2delta, there was very little new Cac activity at all.

How the brain focuses on what's in mind

Working memory, consciously holding and manipulating new information in mind, takes work. In particular, participating neurons in the prefrontal cortex have to work together in synchrony to focus our thoughts, whether we're remembering a set of directions or tonight's menu specials. A Picower Institute study shows how that focus emerges.

The key measure in the study in *Scientific Reports* is the variability of the neurons' activity. Scientists widely agree that less variability of activity means more focused attunement to the task.

In several studies between 2016 and 2018 lead author Mikael Lundqvist and co-senior author Earl K. Miller showed through direct measurements of hundreds of neurons and rigorous modeling that bursts of gamma frequency rhythms in the prefrontal cortex coordinate neural representation of the information held in mind. Bursts of lower frequency beta rhythms, meanwhile, implement the brain's manipulation of that information.

The new study shows that the reduced variability is consistent with this bursting rhythms model of working memory.

"We used actual neural activity recorded from the prefrontal cortex to show that the rhythmic bursts reduce their variability as animals focus on a task," said Miller, Picower Professor at MIT.

In the study, Lundqvist and the team measured gamma bursts and individual neural spiking among hundreds of neurons as six animals played three different working memory games. They analyzed how much that activity varied from trial to trial of each task.

As the animals proceeded through each task, gamma bursts and spiking rates showed clear differences from the pre-task period, consistent with them being modulated by demands of the task. While activity was clearly modulated by the task, so was the variability from trial to trial. The observed reduction of variability was not only true in time, but also in space. Areas of the prefrontal cortex where gamma bursts and spiking represented task information showed much greater decreases in variability than areas that were not representing task information.

Computer modeling showed that reductions in gamma burst variation necessarily led to reductions in individual neuron spiking variation.

Brain wired for the math of stopping on a dime

You are late and you see the bus roll past you. You break into a full sprint to get to the bus as fast as possible and then to stop exactly in front of the doors. To stop quickly and precisely enough, a new MIT study in mice finds, the mammalian brain is niftily wired to implement principles of calculus.

Catching a bus or running right up to a visually indicated landmark to earn a water reward (as the mice did), is a learned, visually guided, goal-directed feat. In such tasks, which are a major interest in the lab of senior author Mriganka Sur, Newton Professor of Neuroscience, the crucial decision to switch from one behavior (running) to another (stopping) comes from the brain's cortex, where the brain integrates the learned rules of life with sensory information to guide plans and actions.

"The goal is where the cortex comes in," Sur said. "Where am I supposed to stop to achieve this goal of getting on the bus?"

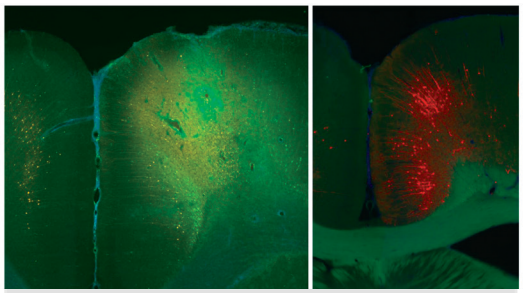
And that's also where it gets complicated. The mathematical models of the behavior that postdoc and study lead author Elie Adam developed predicted that a "stop" signal going directly from the M2 region of the cortex to regions in the brainstem, which actually control the legs, would be processed too slowly.

So how does the brain speed up the process? The researchers show in *Cell Reports* that M2 sends the signal to an intermediary region called the subthalamic nucleus (STN), which then sends out two signals down two separate paths that re-converge in the brainstem. Why? Because the difference made by those two signals, one inhibitory and one excitatory, arriving one right after the other turns the problem from one of integration, which is a relatively slow adding up of inputs, to differentiation, which is a direct recognition of change. The shift in calculus implements the stop signal much more quickly.

Adam's model predicted the speed needed for a proper stop and that differentiation would be necessary to achieve it. A series of anatomical investigations and experimental manipulations confirmed the model's predictions.

When a task adds more steps, this **circuit** helps you notice

Life is full of processes to learn and then relearn when they become more elaborate. One day you log in to an app with just a password, then the next day you also need a code texted to you. Our brains need a way to keep up. Picower Institute scientists have revealed some of the circuitry that helps a mammalian brain learn to add steps.



Researchers traced neurons projecting from the anterior cingulate cortex (right, red) to the motor cortex (left, green).

In *Nature Communications* they showed that when they changed the rules of a task, requiring rats to adjust from performing just one step to performing two, a pair of regions on the brain's surface, or cortex, collaborated to update that understanding and change the rats' behavior to fit the new regime. The anterior cingulate cortex (ACC) appeared to recognize when the rats weren't doing enough and updated cells in the motor cortex (M2) to adjust the task behavior.

Daigo Takeuchi, a researcher at the University of Tokyo led the work as a postdoc at the RIKEN-MIT Laboratory for Neural Circuit Genetics at The Picower Institute directed by senior author and Picower Professor Susumu Tonegawa.

They traced neural circuit connections that led into M2 and found that many originated in the ACC. They began to see the ACC's role in guiding M2's sequential decisions when they instilled a genetic manipulation in ACC cells that allowed them to suppress their activity.

This "chemogenetic" disabling of the ACC had a very specific effect. Compared to rats with normal ACC activity, rats with silenced ACCs failed for much longer to realize when second step had become necessary in the task.

Further evidence painted a clear picture: When the rats needed to notice that an extra step was now required, the ACC's job was to learn from negative feedback and signal M2 to take the second step. If the ACC wasn't available when feedback was provided, then M2 cells that emphasize negative outcomes apparently would become especially active and the rats would fail to do the required second step for a time before finally catching on.

At a **research forefront**, 'post-bacc' scholar looks ahead

Eric Bueno represents the first generation in his family to go to college, but the computer science degree he earned at the University of Connecticut last year has turned out to be just the beginning of what he's on his way to accomplishing in higher education. Now his sights are set on a PhD and becoming the kind of mentor who has helped him along the way.

"Growing up in the Hartford school district taught me how to make a lot with a little," Bueno said.

As a kid, he said, he found that math and science provided reassuringly concrete answers and so he seized opportunities to learn about robotics in the Academy of Engineering and Green Technology within Hartford Public High School and to participate in UConn's College Access and Preparation (UCAP) program, which offered classes and residence at the university each summer.

"That was a way to get students some college experience because being first generation you don't really get that kind of direction from say, your parents or your siblings," Bueno said. "That's where I realized I wanted to continue going to school after high school.

"Now I'm hoping to pursue a PhD."

Bueno committed himself to pursuing a doctorate earlier this summer as he reached the midpoint of his two-year term in the Research Scholars Program (RSP), a post-baccalaureate opportunity in the Department of Brain and Cognitive Sciences (BCS) at MIT. The program, funded by several sources including The Picower Institute, is designed to provide outstanding recent college graduates from historically underrepresented minority groups and/or economically disadvantaged backgrounds with additional academic training, as they earn a full graduate-level stipend, to become competitive PhD applicants. Right now five scholars, including Bueno, are in BCS labs. Another group of five will join BCS this fall, including in two Picower labs.

Bueno works with Associate Professor Steven Flavell, who studies how the nervous system produces long-lasting but flexible internal and behavioral states. Flavell has been seeking a way to reliably track the activity of every one of the 190 or so neurons in the brains of *C. elegans* worms as they freely move around and behave for minutes or even hours at a time. It's a fiendishly difficult problem to make a system that will reliably distinguish each cell, every fraction of a second, no matter where and how the worm moves.

Bueno and Flavell might have a solution using a strain of worms engineered at Columbia University in which each neuron can fluoresce with a unique combination of three different colors. Varying relative levels of those colors composes unique hues, and therefore color "barcodes" for each cell. The Flavell lab is doing some extra engineering to use this strain in experiments where the worms can continue to exhibit a full range of behaviors.

Determining how neurons across the *C. elegans* brain change activity during free behavior is allowing the Flavell lab to gain fundamental insights into how the nervous system generates behavior. But before the computer can reliably associate each barcode with each cell in a moving animal, Bueno is working to do so manually, creating a reference set of images that can teach the computer. Along the way, he's making it easier for the machine, for instance by writing code that corrects each image to account for bleaching caused by the lasers that make the fluorescent effect occur, and warping (or, registering) the images so that they can all be aligned.

"We have been extremely fortunate to have Eric in the lab," Flavell said. "Eric came to us with extensive computational skills and intellect, and he has applied those tools wonderfully to neuroscience.

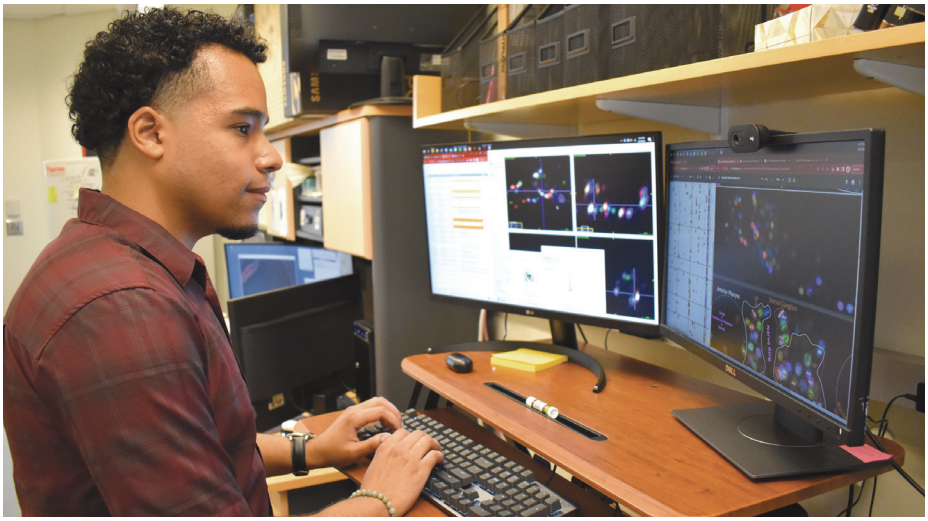
"It is challenging to run all of the complex image analysis tools and labeling strategies needed to pull this off, but Eric has an extraordinary ability to put this all together."

Bueno said he'd like to put his increasing skills and education to use mentoring others.

"I'm a product of so many different mentors throughout my life," he said. "I've seen a lot of people kind of go down different paths that may not be the best choices. I could have very easily been one.

"Having been raised in Hartford, where I would say you can really go either way, it just taught me the importance of having that kind of figure who can kind of help you figure out what was important to you and how you can find that in a really constructive way."

Today he's gaining skills, knowledge, experience and mentoring in the RSP. Tomorrow he might be providing all those things for a next generation of scholars.



High schoolers' summer starts with extra exposure to science

On June 21, their last day of school, 17 high school students from Lawrence did not have to come tour life sciences research labs around MIT. They were just eager to seize the opportunity, provided by their school and The Picower Institute, to learn more about science and medicine, said teacher Rebecca Veilleux.

It was the same for another 20 Everett High School students in the SEED Pathway program, who opted for a morning full of exposure to cutting edge research to build a foundation of understanding about possible science careers.

"It helps them focus on the different fields of STEM they could choose," said Everett Academy Lead Teacher Nancy Cianchetta. "It helps them learn about more than what I could expose them to in just the classroom."

For instance, a group of her students got the chance to tour the stem cell facility that the lab of Picower Institute Director and Picower Professor Li-Huei Tsai relies upon to do cutting edge research on Alzheimer's disease. There, postdocs Adele Bubnys and Rebecca Pinals showed the students how they can transform a person's skin cells into multicellular, 3D brain tissue cultures that model important features of Alzheimer's such as the buildup of amyloid plaques.

"You can make any cell type from anyone," Bubnys said, explaining that the lab induces the skin cells to become stem cells and then transforms those in to neurons, brain blood vessels, immune cells and more, creating powerful lab models of human brains not only for studying disease, but also testing whether drugs can get across the blood-brain barrier that strictly filters what goes in or out of brain tissue.

At the same time, a group of the Lawrence students were visiting in the lab of Picower Professor Mark Bear to learn how postdoc David Stoppel and graduate student Max Heinrich study autism in mice modeling human genetic mutations.

The scientists showed the students how they can take a slice of a mouse's brain, mount it under a microscope and then electrically stimulate neurons and measure their electrical response. Importantly, they said, cells in the brains of mice with a particular gene knocked out are hyperactive compared to cells from control mice where the gene has been left unaffected.

Just before a pizza lunch, a few of the Lawrence students broke off from the pack to tour the fruit fly lab of Menicon Professor Troy Littleton, where researchers study how neurons communicate with each other and with muscles. There, Payton Dupuis and Katherine Gourianova, undergraduates visiting as part of the Bernard S. and Sophie G. Gould MIT Summer Research Program in Biology, gave the students a closeup look at male and female flies and how flies are dissected for study in the lab.

Meanwhile, other students from each high school continued to talk about Alzheimer's research with Pinals and Bubnys from the Tsai lab.

In all, throughout a rich morning of tours organized by Mandana Sassanfar, Diversity and Outreach Coordinator in the Departments of Biology and Brain and Cognitive Sciences, groups of the students also toured the Whitehead Institute, the Biology department, The McGovern Institute's Martinos Imaging Center, and the Koch Institute for Integrative Cancer Biology.

Lawrence students Darianna Sanchez and Jayden Rosario said they enjoyed learning more about a project at the Koch Institute where they saw how engineered beads can help improve drug delivery. Sanchez also liked the fruit fly demonstration.

Classmates Ethan Santiago and Evelyn Brito said they found it cool that Heinrich and Stoppel in the Bear lab could take a slice out of a brain and still keep it alive and active enough to make meaningful measurements.

Brito said she doesn't necessarily have a career doing that in mind, per se, but that she just wanted to come to MIT for the experience.

"I just wanted to learn new things," she said.

Even on the last day of school.

Students from Lawrence High School listen to Bear Lab graduate student Max Heinrich describe his autism research.
Image credit: David Orenstein

Tsai Lab Postdoc Rebecca Pinals demonstrates stem cells to Everett High School students.
Image credit: Mandana Sassanfar

Visiting undergraduate Payton Dupuis (seated) explains the Littleton Lab's fruit fly research to Everett high school students.
Image credit: Mandana Sassanfar

To the Clinic!

When fundamental research yields discoveries with medical potential, Picower Institute professors find ways to test whether they'll help patients.

A few years ago, working with mice, Gloria Choi and colleagues discovered a molecular and circuit basis for how certain genetic abnormalities or maternal infection during pregnancy may lead to an increased risk of autism-like social behavior deficits in offspring. But a huge question remained: Are the processes occurring in humans?

There were certainly reasons to think so. The original association between maternal infection and autism risk in progeny had been established in humans and the genetic anomalies engineered into the mice also were first discovered in patients. Choi's mouse studies pinpointed aberrant development and hyperactivity in the S1DZ area of the mouse somatosensory cortex. S1DZ is analogous to, but not exactly the same as, the "3a" region of the same cortex in humans. To know for sure whether the mechanisms of action in mice are also at play in humans would require studying children, not mouse pups.

Starting a human study is not easy but fortunately, one of Korea's foremost autism physicians was visiting around the corner at the Broad Institute. Dr. Hyo-Won Kim took the short walk to Choi's office to meet about forging the collaboration needed to answer the question. Today they are enrolling patients at Asan Medical Center in Seoul to conduct MRI scans that will confirm or refute the hypothesis that hyperactivity in the 3a region is afoot in human autism patients. If that proves true, then treatments to reduce hyperactivity in the region might provide a meaningful benefit. For instance, Choi has found that the immune system cytokine IL-17a can reduce hyperactivity in S1DZ.

Though Choi had never launched a human study before, she says she felt compelled to seize the opportunity.

"The brains of rodents are very different from the brains of humans," said Choi, Mark Hyman Jr. Associate Professor of Neurobiology. "In order to make these findings worth it and mean something, we have to show it also happens in humans, too. I had no other choice but to pursue it."

Indeed though The Picower Institute focuses on fundamental neuroscience research, several members of the faculty, upon making discoveries with clear clinical potential, have pursued a variety of approaches to ensure that the medical value of the discoveries is clinically investigated in humans.

"All routes are open to us," said Picower Professor Mark Bear, who has both launched companies and forged clinical collaborations to develop therapies and diagnostics based on his research.

Testing in-house

For Choi a serendipitous connection became an external clinical collaboration, but for Picower Professor Li-Huei Tsai, a similar circumstance led to a different approach: building an in-house clinical testing team.

In 2016 Tsai's lab showed in mice that stimulating 40Hz "gamma" frequency brain rhythms with light flashing at that same frequency could reduce the buildup of Alzheimer's pathology in the brains of mice. This caught the attention of neurologist Diane Chan who had been in touch with the lab about a fellowship.

"She became very excited about translating the animal results to human subjects," Tsai said. "It was perfect timing"

And so Tsai and Chan created a group within the Tsai lab, the "Human Gamma Team," to develop 40Hz stimulation devices, recruit volunteers, and design and carry out clinical studies of the potential therapy. One crucial attribute that made doing so easier is that the method is completely non-invasive, unlike a drug or an implanted device.

Last year they posted a pre-print study showing encouraging preliminary results from combining light and sound stimulation in human patients in a double-blinded, controlled pilot study. Compared to people who started out receiving the placebo version, people who got 40Hz stimulation for an hour a day for several weeks showed reduced atrophy of the hippocampus, better synchrony and connectivity between brain regions, improved sleep, and better performance on a face-name association memory test.

It was a huge change for the Tsai lab to expand to clinical studies, but like Choi, Tsai wanted to directly test her discovery's medical potential.

"There are so many treatments that cure Alzheimer's in mouse models but essentially all of them fail in humans," Tsai said. "In the end how relevant is the scientific discovery in the most strict sense and critical sense? It has to be validated in humans."

The team is now embarking on new studies. Can the stimulation prevent the onset of cognitive impairment? Can it benefit patients with Parkinson's disease? What about Down syndrome? With an in-house, physician-led team, Tsai can readily ask these new questions even as the rest of her lab continues more fundamental Alzheimer's related research.

Founding a new center

As an anesthesiologist practicing at Massachusetts General Hospital (MGH), Emery N. Brown, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience, has a built-in opportunity to translate his fundamental neuroscience and statistics research to clinical practice, but for a long time he kept the two worlds separate. Around 2005, though, he started to apply his research analyzing neuroscience data to his work in the operating room, breaking through a traditional barrier.

"Anesthesia is not viewed as part of neuroscience," he said. "It's viewed as a part of clinical pharmacology."

But a significant part of anesthesiology is controlling the brain's arousal state and the body's pain state, not just getting chemicals into cells so they'll be metabolized.

Brown's studies have shown that different anesthetic drugs produce distinct "signature" patterns of rhythms when people are unconscious. The patterns vary characteristically with drug mechanism of action, dose, the patient's age and the patient's state of health. These insights allowed him to use EEG-based brain rhythm monitoring in the OR to directly assess the unconsciousness of his patients. In this way he can more precisely control drug dosing so that patients experience the benefits of general anesthesia without any overdosing that could cause post-operative side-effects like nausea, vomiting or brain dysfunction.

Understanding how anesthesia and arousal control work on a systems neuroscience level opens up many possibilities for improving patient care, Brown says. To explore those he is working to found a new center spanning MIT and MGH called the Brain Arousal State Control Innovation Center, or BASCIC. He and colleagues envision no less than six basic science or clinical studies based on fundamental neuroscience research: Waking patients after anesthesia by activating specific arousal pathways; testing a specific anesthetic as a sleep aid; using anesthetics to develop a treatment for Alzheimer's; developing a closed-loop system for measuring brain rhythms and automatically adjusting anesthetic dose; testing an anesthetic as an antidepressant; and treating brain arousal pathways to stimulate coma recovery.

BASCIC, as a center, could help to seed fund and administrate all these studies.

Leveraging the marketplace

Bear, too, has been working to test and develop fundamental discoveries with therapeutic potential for more than a decade. Sometimes the marketplace is the best place to try that, especially given the significant financial resources that late-stage trials require. Bear is well known, for instance, for having co-founded Seaside Therapeutics to spur development and testing of a promising treatment his lab discovered for Fragile X syndrome, a genetically caused form of autism. Though that specific effort fell just short in a high-profile phase III trial, he has recently started a new company, Allos Pharma Inc., to continue development and testing.

In parallel with her in-house clinical testing, Tsai also co-founded Cognito Therapeutics to spur larger-scale testing and development of 40Hz sensory stimulation. Earlier this year the company launched phase III clinical trials.

Bear is also now weighing how best to bring to the clinic another therapeutic strategy developed in his lab. They have shown in multiple animal models that the common vision disorder amblyopia can be overcome, even in adulthood, by briefly anesthetizing the unaffected eye. That essentially "reboots" the level of visual activity needed to strengthen connections in the brain serving the impaired eye. In the year since his lab published highly encouraging results, he has heard strong interest both from eye specialists and also from an ophthalmology company about bringing it to people. He has spoken extensively with the potential clinical collaborators and has met twice with the company.

"We have a number of irons in the fire," Bear said.

To advance the therapy, the company would license the patent from MIT and develop and test a treatment based on it. Tsai has done that with another of her Alzheimer's discoveries. Inhibiting an enzyme called HDAC2, which becomes overactive in Alzheimer's, restores the ability of neurons to forge connections that sustain learning and memory. That was licensed by a company called Rodin Therapeutics.

Newton Professor Mriganka Sur has also watched a company advance one of his therapeutically relevant discoveries. Over 15 years ago, his lab showed that IGF-1 is required to promote maturation of synaptic connections in the cerebral cortex. In 2009, studying mice modeling the mutation that causes Rett syndrome, they showed that the disease causes the brain's connections to remain immature into adulthood, but administering the peptide form of IGF-1 had substantial therapeutic benefits for neurological and non-neurological symptoms of the disorder. A company developed an oral formulation to prolong the molecule's bioavailability, which Sur supported because of the urgent need for a therapy to reach patients. Starting in 2014, the company successfully completed phase I and II trials in human patients, and late last year, they announced success of a phase III trial. In July this year, they asked the FDA to approve the treatment.

That decision is pending, but if the FDA says yes, IGF-1 for Rett syndrome could become the first example of a Picower-discovered therapy to turn into a medicine, going all the way down the long, complicated road from lab bench to patient bedside.

In different ways, Picower faculty have advanced and enabled clinical application of fundamental work.

Picower Picnic

Scores of Picower Institute members brushed aside scorching temperatures August 9 to tie-dye shirts, play lawn games and have lunch and ice cream together with friends and colleagues on MIT's Kresge Oval. The Picower Community Picnic offered a break from work and a relaxed chance to make new connections, but at least when everyone went back it was to air conditioning.

We thank Wendy Fisher and her siblings who in 2008 established an endowment at the Picower Institute honoring their parents and creating the annual Dana and Betty Fisher Retreat.

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