From Biological Intelligence To artificial Intelligence

How basic neuroscience research by Picower faculty has mattered to AI

Pg. 9

Neuroscience News

FALL 2020

THE PICOWER INSTITUTE FOR LEARNING AND MEMORY

DIRECTOR'S **MESSAGE**

Dear Friends,

In this edition we are proud to report on 10 new papers. This abundance of articles spans an array of topics ranging from insights into Alzheimer's disease, Huntington's disease and Fragile X syndrome, to new technologies, to fundamental findings about how the brain understands the space around us and coordinates motion and behaviors. And in our cover story (see p. 9) we also examine how some of our faculty's work over the years has led to exciting and sometimes unexpected intersections with the field of Artificial Intelligence.

Though it is a pleasure to share our research and to reflect on how it may help advance science and technology, we remain mindful of the difficulties that the Covid-19 pandemic continues to bring. Circumstances remain troubling, but we are encouraged that in early August we reached a new milestone in ramping research back up. Maintaining strict distancing and safety protocols, we are now operating at 50 percent of normal hours in the lab, following a successful ramp up to 25 percent time in June. Meanwhile, we all continue to be as productive as possible when remote.

At the same time we have been working earnestly with our colleagues across Building 46 and around MIT to achieve new progress in improving diversity, equity and inclusion in our institutions. After searing incidents of racial injustice nationally this spring, MIT's brain science community is responding by committing to several specific new steps and a process for further changes to combat systemic racism and increase outreach and allyship with underrepresented minorities in the sciences (see p. 8).

We are also persisting as an academic community via a busy calendar of symposia this fall, featuring talks by leading researchers in neurodegeneration, internal brain states, and Down syndrome. Because these stimulating events will occur online, they are easier than ever to attend. See page 11 and picower.mit.edu/events for details.

Thank you for engaging with us, be it through these events, by perusing the pages that follow, or many other ways as we continue our work together.

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

Study addresses **Alzheimer's** blood-brain barrier impairment

By developing a lab-engineered model of the human blood-brain barrier (BBB), Picower Institute neuroscientists have discovered how the most common Alzheimer's disease risk gene variant causes amyloid protein plaques to disrupt the brain's vasculature, and showed they could prevent the damage with medications already approved for human use. Results appeared in *Nature Medicine.*

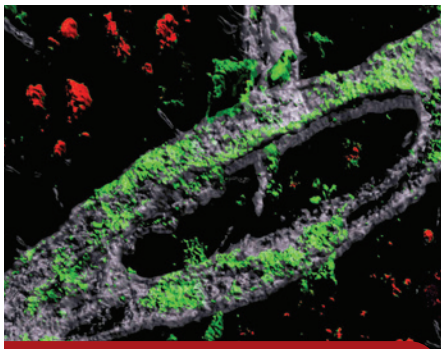
About 25 percent of people have the APOE4 variant of the APOE gene, which puts them at greater risk for Alzheimer's disease. Almost everyone with Alzheimer's, and even some elderly people without, suffer from cerebral amyloid angiopathy (CAA) in which amyloid deposits on blood vessel walls impair the BBB's ability to properly transport nutrients, clear waste and block out pathogens and unwanted substances.

To investigate the connection between Alzheimer's, the APOE4 variant and CAA, lead author Joel Blanchard, a postdoc in the lab of Picower Institute director Li-Huei Tsai, coaxed human induced pluripotent stem cells to become the three types of cells that make up the BBB: brain endothelial cells, astrocytes and pericytes. Pericytes were modeled by mural cells that they tested extensively to ensure they exhibited pericyte-like properties and gene expression.

Grown for two weeks within a three-dimensional hydrogel scaffold, the BBB model cells assembled into vessels that exhibited natural BBB properties, including low permeability to molecules and expression of the same key genes, proteins and molecular pumps. When immersed in culture media high in amyloid proteins, mimicking conditions in Alzheimer's brains, the lab-grown BBB models exhibited amyloid accumulation as in human disease.

In their models, the team found that pericyte-like mural cells with the APOE4 variant churned out too much APOE protein, Tsai said.

The team also looked at APOE expression in samples of human brain vasculature in the prefrontal cortex and the hippocampus, two regions crucially affected in Alzheimer's. Consistent with the team's BBB model, people with APOE4 showed higher expression of the gene in the vasculature, specifically in pericytes.



A 3D rendering of an APOE4-carrying engineered blood vessel shows heavy accumulation of amyloid protein (green).

"That is a salient point of this paper," said Tsai, a founding member of MIT's Aging Brain Initiative. "It's really cool because it stresses the cell-type specific function of APOE."

APOE causes amyloid proteins, which are more abundant in Alzheimer's, to clump together.

But why was APOE4 so overexpressed by pericytes? The team identified hundreds of transcription factors – proteins that determine how genes are expressed – that were regulated differently between APOE3 and APOE4 pericyte-like mural cells. Then they looked at which factors specifically impact APOE expression. A set that was upregulated in APOE4 cells stood out: ones in the calcineurin/NFAT pathway. They observed similar upregulation of the pathway in pericytes from human hippocampus samples.

There are already drugs that suppress the pathway. They are used to subdue the immune system after a transplant. When the researchers administered cyclosporine A or FK506 to the lab-grown BBBs with the APOE4 variant, they accumulated much less amyloid than untreated ones did. They also tested the drugs in APOE4-carrying mice. The medicines reduced APOE expression and amyloid buildup.

Blanchard and Tsai noted that the drugs can have significant side effects, so their findings might not suggest using exactly those drugs to address CAA in patients.

"Instead it points toward the value of understanding the mechanism," Blanchard said. "It allows one to design a small molecule screen to find more potent drugs that have less off-target effects."

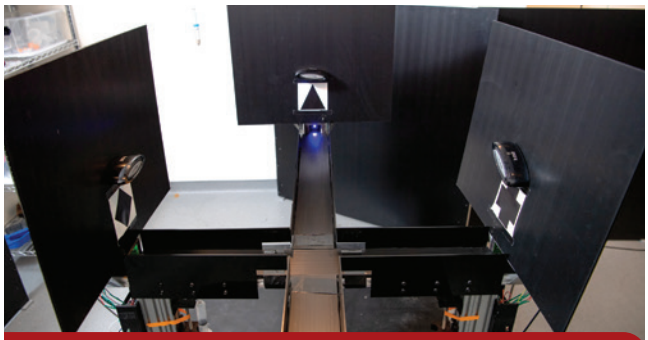
Animals infer contexts probabilistically, study suggests

The brain creates a new map for every unique spatial context – for instance, a different room or maze. But scientists have struggled to learn how animals decide when a context is novel enough to merit creating, or at least revising, these mental maps. In a study in *eLife,* MIT and Harvard researchers propose a new understanding: The process of "remapping" can be mathematically modeled as a feat of probabilistic reasoning by the rodents.

The approach offers scientists a new way to interpret many experiments that depend on measuring remapping to investigate learning and memory. Remapping is integral to that pursuit, because animals (and people) associate learning closely with context, and hippocampal maps indicate which context an animal believes itself to be in.

"People have previously asked 'What changes in the environment cause the hippocampus to create a new map?' but there haven't been any clear answers," said lead author Honi Sanders. "It depends on all sorts of factors, which means that how the animals define context has been shrouded in mystery."

Sanders is a postdoc in the lab of Sherman Fairchild Professor Matthew Wilson. The pair collaborated with Samuel Gershman, a Harvard psychology professor.



A maze in the Wilson lab. *Photo by Peter Goldberg*

Fundamentally a problem with remapping that has led labs to report conflicting, confusing, or surprising results, is that scientists cannot simply assure their rats that they have moved from experimental Context A to Context B, or that they are still in Context A, even if some ambient condition, like temperature or odor, has inadvertently changed. It is up to the rat to explore and infer that conditions have or have not changed enough to merit remapping.

So rather than trying to understand remapping measurements based on what the experimental design is supposed to induce, the authors argue that scientists should predict remapping by mathematically accounting for the rat's reasoning using Bayesian statistics, which quantify the process of starting with an uncertain assumption and then updating it as new information emerges.

The trio call their approach "hidden state inference" because to the animal, the possible change of context is a hidden state that must be inferred.

In the study the authors describe several cases in which hidden state inference can help explain the remapping, or the lack of it, observed in prior studies.

How the brain remains stable, reliable amid noise and variation

How does the brain overcome unpredictable and varying disturbances to produce reliable and stable computations? A new study by MIT neuroscientists provides a mathematical model showing how such stability inherently arises from several known biological mechanisms.

More fundamental than the willful exertion of cognitive control over attention, the model the team developed describes an inclination toward robust stability that is built in to neural circuits by virtue of the connections, or "synapses" that neurons make with each other. The equations they derived and published in *PLOS Computational Biology* show that networks of neurons involved in the same computation will repeatedly converge toward the same patterns of electrical activity, or "firing rates," even if they are sometimes perturbed by the natural noisiness of individual neurons or arbitrary sensory stimuli the world can produce.

To develop the model, the lab of Picower Professor Earl Miller joined forces with colleague Jean-Jacques Slotine, professor of brain and cognitive sciences and mechanical engineering. Slotine brought the mathematical method of "contraction analysis" to the problem along with tools his lab developed to apply the method. Contracting networks exhibit the property of trajectories that start from disparate points ultimately converging into one trajectory, like tributaries in a watershed. They do so even when the inputs vary with time. They are robust to noise and disturbance, and they allow for many other contracting networks to be combined together without a loss of overall stability – much like the brain typically integrates information from many specialized regions.

Graduate student Leo Kozachkov led the study. What he found is that the variables and terms in the model's equations that enforce stability directly mirror properties and processes of synapses: inhibitory circuit connections can get stronger, excitatory circuit connections can get weaker, both kinds of connections are typically tightly balanced relative to each other, and neurons make far fewer connections than they could.

The team is considering how the models may inform understanding of different disease states of the brain. Aberrations in the delicate balance of excitatory and inhibitory neural activity in the brain is considered crucial in epilepsy, Kozachkov notes. A symptom of Parkinson's disease, as well, entails a neurally-rooted loss of motor stability. Miller adds that some patients with autism spectrum disorders struggle to stably repeat actions (e.g. brushing teeth) when external conditions vary (e.g. brushing in a different room).

Neural vulnerability in **Huntington's** tied to mitochondrial RNA

Picower Fellow Hyeseung Lee and Associate Professor Myriam Heiman working together in the lab. *Photo by Peter Goldberg*

In the first study to comprehensively track how different types of brain cells respond to the mutation that causes Huntington's disease (HD), MIT neuroscientists found that a significant cause of death for an especially afflicted kind of neuron may be an immune response to genetic material errantly released by mitochondria, the cellular components that provide cells with energy.

The researchers measured how levels of RNA differed from normal in brain samples from people who died with HD and in mice engineered with various degrees of the genetic mutation. They found that RNA from mitochondria were misplaced within the brain cells, called spiny projection neurons (SPNs), that are ravaged in the disease, contributing to its fatal neurological symptoms. The scientists observed that these stray RNAs, which look different to cells than RNA from the cell nucleus, triggered a problematic immune reaction.

"When these RNAs are released from the mitochondria, to the cell they can look just like viral RNAs and this triggers innate immunity and can lead to cell death," said Associate Professor Myriam Heiman.

Picower Fellow Hyeseung Lee and former visiting scientist Robert Fenster are co-lead authors of the study in *Neuron.*

The team's screening methods not only picked up the presence of mitochondrial RNAs most specifically in the SPNs but also showed a deficit in the expression of genes for a process called oxidative phosphorylation that fuel-hungry neurons employ to make energy. The mouse experiments showed that this downregulation of oxidative phosphorylation and increase in mitochondrial RNA release both occurred very early in disease.

Moreover, the researchers found increased expression of an immune system protein called PKR, which has been shown to be a sensor of the released mitochondrial RNA. In fact, the team found that PKR was not only elevated in the neurons, but also activated and bound to mitochondrial RNAs.

The study produced several other potentially valuable findings, Heiman said.

One is that the study produced a sweeping catalog of substantial differences in gene expression, including ones related to important neural functions such as their synapse circuit connections and circadian clock function. Another is that a master regulator of these alterations may be the retinoic acid receptor b (or "Rarb") transcription factor. This could be a clinically useful finding because there are drugs that can activate Rarb.

Immune molecule has complex role in Huntington's

More than a decade before people with Huntington's disease show symptoms, they can exhibit abnormally high levels of an immune-system molecule called interleukin-6 (IL-6), which has led many researchers to suspect IL-6 of promoting the eventual neurological devastation associated with the genetic condition. A new investigation shows the story likely isn't so simple. MIT reseearchers found that Huntington's model mice bred to lack IL-6 showed exacerbated symptoms compared to HD mice that still had it.

"If one looks back in the literature of the Huntington's disease field many people have postulated that reductions to IL-6 would be therapeutic in HD," said Associate Professor Myriam Heiman, senior author of the paper in *Molecular Neurodegeneration*. Former postdoc Mary Wertz is the lead author.

To test the hypothesis the researchers crossbred mice engineered to model HD with mice engineered to lack IL-6. They then compared the performance of offspring on a variety of standard movement tasks to that of healthy mice, mice just lacking IL-6, and mice just modeling HD but still having IL-6. The HD mice lacking IL-6 performed significantly worse than the other mouse lines, including the HD mice that still had IL-6.

Struck by the findings, the team sought to understand why they occurred. To do that, they measured gene expression in all the major cell types in the striatum, the brain region most affected in HD, by sequencing RNA in thousands of individual cells in each mouse line. When they looked at the differences in gene expression in neurons between the two HD mouse lines – the ones that had IL-6 and the ones that didn't – they saw that many genes important for synapses, the connections that link neurons into circuits, were significantly less expressed in the HD mice without IL-6.

"Perhaps this worsening of the phenotype is due to perturbation of those synaptic signaling pathways," Heiman said.

While the study shows there is definitely not a therapeutic benefit to completely knocking out IL-6, it may still be possible to find a level between overexpression and complete knockout that is therapeutic, Heiman said.

Surprising study of synapse size, strength yields **autism** insight

A new study reveals surprises about basic mechanisms of how neural connections, called synapses, change to enable learning and memory. Understanding them, the research suggests, could yield new treatments for a disorder called Fragile X that causes autism.

Synapses can either get stronger or weaker and the tiny spine structures that support them can get bigger or smaller. The field's assumption has been that these functional and structural changes, forms of "synaptic plasticity," correlate. But the study in *Molecular Psychiatry* supports a newer view that those associations do not always hold.

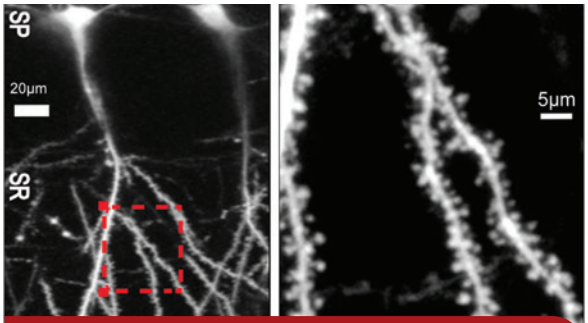
"We saw these breakdowns of correlation between structure and function," said Picower Professor Mark Bear. "One conclusion is you can't use spine size as a proxy for synaptic strength – you can have weak synapses with big bulbous spines."

The study's co-lead authors are former lab members Aurore Thomazeau and Miquel Bosch.

The team stimulated plasticity via two different neural receptors (called mGluR5 and NMDAR) under two different conditions (neurotypical rodents and ones engineered with the mutation that causes Fragile X).

Activating mGluR5 receptors induced weakening, called long-term depression (LTD), but did not lead to any spine shrinkage in either Fragile X or control mice. In other words, functional change was not accompanied by structural change.

With NMDARs, the two forms of plasticity occurred together, both in control and fragile X rodents, but apparently by different means. Blocking ions in the NMDAR synapses only prevented the weakening, not the shrinking. To prevent shrinking in control rodents, the researchers had to inhibit protein synthesis.



Neurons from the hippocampus region of a rodent brain (left); A zoomed in section of the neural dendrites show spines where many synaptic connections with other neurons are formed. *Image by Stephanie Barnes.*

Yet another finding may provide new hope for treating Fragile X.

When the team tried to prevent spines from shrinking via NMDAR in Fragile X rodents by inhibiting protein synthesis (like they did in the controls), they found it didn't work. It was as if there was already too much of some protein that promotes the shrinkage. It's therefore important to identify that conjectured protein, which Bear has begun to refer to as "protein X."

"The question is what is protein X," Bear said. "The evidence is quite strong that there is a rapidly turned over protein X that is wreaking havoc in Fragile X. Now the hunt is on. We'll be really excited to find it."

Similar neurons show distinct styles via their connection to muscle

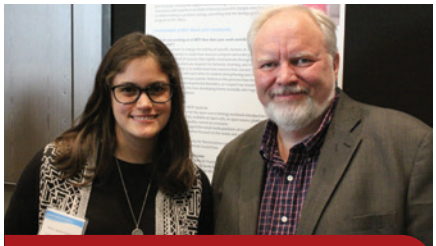
MIT neuroscientists studying how seemingly similar neuronal subtypes drive locomotion in the fruit fly found a dramatic difference: While one neuron scrambled to adjust to different changes by the other, it received no requital in response when circumstances were reversed.

The *Journal of Neuroscience* study suggests that these subclasses of neurons, which are also found abundantly in people and many other animals, exhibit a previously unappreciated diversity in their propensity to respond to changes, a key property known as "synaptic plasticity." Synaptic plasticity is considered an essential mechanism of how learning and memory occur in the brain, and aberrations are likely central to disorders such as autism.

"By seeing that these two different types of motor neurons actually show very distinct types of plasticity, that's exciting because it means it's not just one thing happening," said Troy Littleton, Menicon Professor of Neuroscience. "There's multiple types of things that can be altered to change connectivity within the neuromuscular system."

Both of the neurons work in the same way, by emitting the neurotransmitter glutamate onto their connections, or synapses, with the muscles. But these two neurons do so with different styles. The "tonic" neuron, which connects only to a single muscle, emits its glutamate at a constant but low rate while the muscle is active. Meanwhile, the "phasic" neuron connects to a whole group of muscles and jumps in with a strong quick pulse of activity to spring the muscles into action.

To conduct the study, lead author Nicole Aponte-Santiago developed the means to tailor genetic alterations specifically in each of the two neurons. She then employed two manipulations of each neuron. She either wiped them out completely by making them express a lethal protein called "reaper" or she substantially tamped down their glutamate activity via expression of tetanus toxin.



Nicole Aponte-Santiago and Troy Littleton at a ceremony in 2019 where Aponte-Santiago was honored as a Graduate Woman of Excellence

When she wiped out the phasic neuron, the tonic neuron quickly stepped up its signaling, attempting to compensate. But in flies where she wiped out the tonic neuron, the phasic neuron didn't budge at all, continuing as if nothing had changed. Similarly when she reduced the activity of the phasic neuron with the toxin, the tonic neuron produced more components in its synapses in response. But when she reduced the activity of the tonic neuron the phasic neuron again didn't appear to respond.

Dopamine helps circuits coordinate motor behaviors

For a nematode worm, a big lawn of the bacteria that it eats is a great place for it to disperse its eggs so that each hatchling can emerge into a nutritive environment. That's why when it speedily roams about a food patch it methodically lays its eggs as it goes. A new study investigates this example of action coordination – where egg-laying is coupled to the animal's roaming – to demonstrate how a nervous system coordinates distinct behavioral outputs.

"All animals display a remarkable ability to coordinate their diverse motor programs, but the mechanisms within the brain that allow for this coordination are poorly understood," noted the scientists, including Steven Flavell, Lister Brothers Career Development Assistant Professor.

Flavell lab members Nathan Cermak, Stephanie Yu, and Rebekah Clark were co-lead authors of the study in *eLife*.

To study how animals coordinate their motor programs, the team invented a new microscopy platform capable of taking sharp, high-frame-rate videos of nematodes for hours or days on end. Guided by custom software, the scope automatically tracks the worms, allowing the researchers to compile information about each animal's behavior. The team also wrote machine vision software to automatically extract information about each of the C. elegans motor programs – locomotion, feeding, egg-laying, and more – from these videos, yielding a near-comprehensive picture of each animal's behavioral outputs.

By using this system and then analyzing the data, Flavell's team was able to identify for the first time a number of patterns of nematode behavior that involve the coordination of multiple motor actions, such as locomotion and egg laying. Flavell's team decided to investigate how the worm's nervous system couples motor programs together. Via a series of experiments in which they methodically manipulated different genes and circuits, they showed that the coordination hinged on the neurotransmitter dopamine, which is abundant in all animals including humans.

They found that a neuron called PDE could sense the presence of food and integrate that with the worm's own motion, generating an activity pattern that essentially reports how quickly worms are progressing through their nutritive environment. The release of dopamine by this neuron, and potentially others as well, could relay this information to the egg-laying circuit, allowing for coordination between the behaviors.

An image of a nematode captured by the team's new microscope. The blue line is the worm's centerline as reconstructed from a spline-based 14-parameter representation.

'ELAST' makes tissues elastic and lasting for easier imaging

To make imaging cells and molecules in the brain and other large tissues easier while also making samples tough enough for years of handling in the lab, Picower Institute engineers have come up with a chemical process that makes tissue stretchable, compressible and pretty much indestructible.

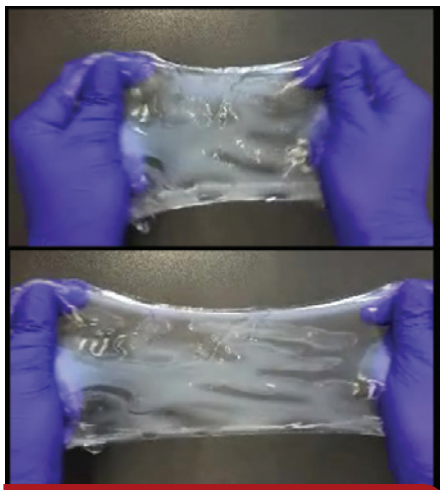
"ELAST" technology, described in a new paper in *Nature Methods*, provides scientists a very fast way to fluorescently label cells, proteins, genetic material and other molecules within brains, kidneys, lungs, hearts and other organs. That's because when such tissues can be stretched out or squished down thin, labeling probes can infuse them far more rapidly. Several demonstrations in the paper show that even after repeated expansions or compressions to speed up labeling, tissues snap back to their original form unaltered except for the new labels.

The lab of Associate Professor Kwanghun Chung developed ELAST amid work on a five-year project, funded by the National Institutes of Health, to make the most comprehensive map yet of the entire human brain. That requires being able to label and scan every fine cellular and molecular detail in the thickest slabs possible to preserve 3D structure. It also means the lab must be able to keep samples perfectly intact for years, even as they must accomplish numerous individual rounds of labeling quickly and efficiently. Each round of labeling – maybe a particular kind of neuron one day, or a key protein the next – will tell them something new about how the brain is structured and how it works.

"When people donate their brain, it is like they are donating a library," said Chung. "Each one contains a library worth of information. You cannot access all the books in the library at the same time. We have to repeatedly be able to access the library without damaging it. Each of these brains is an extremely precious resource."

Former lab postdoc Taeyun Ku, now an assistant professor at the Korea Advanced Institute of Science and Technology, is the study's lead author.

The team's efforts to engineer ELAST came down to finding the right formulation of a gel-like chemical called polyacrylamide. It embeds tissue in an entanglement of long polymer chains with links that are able to slip around, giving the gel a structural integrity but with great flexibility.



An ELASTicized slab of human brain tissue becomes highly stretchable.

Brain region emphasizes reward location

We are free to wander but usually when we go somewhere it's for a reason. A new study shows that as we pursue life's prizes, a region of the brain tracks our location with an especially strong predilection for the location of the reward. This pragmatic bias of the lateral septum suggests it's a linchpin in formulating goal-directed behavior.

"It appears that the lateral septum is, in a sense, 'prioritizing' reward-related spatial information," said Hannah Wirtshafter, lead author of the study in *eLife* and a former graduate student in the lab of senior author Matthew Wilson, Sherman Fairchild Professor of Neurobiology.

Last year, the researchers analyzed measurements of the electrical activity of hundreds of neurons in the LS and the hippocampus, a region known for encoding many forms of memory including spatial maps, as rats navigated a maze toward a reward. In an earlier paper they reported that the LS directly encodes information about the speed and acceleration of the rats as they navigated through the environment.

The new study continued this analysis, showing that while the LS dedicates a much smaller proportion of its cells to encoding location than does the hippocampus, a much larger proportion of those cells respond when the rat is proximate to where the reward lies. Moreover, as rats scurried toward the reward point and back again within the H-shaped maze, the pace of their neural activity peaked closest to those reward locations, skewing the curve of their activity in association with where they could find a chocolate treat. Finally, they found that neural activity between the hippocampus and the LS was most highly correlated among cells that represented reward locations.

"Understanding how reward information is linked to memory and space through the hippocampus is crucial for our understanding of how we learn from experience, and this finding points to the role the lateral septum may play in that process," Wilson said.

Wilson and Wirtshafter said the two studies suggest that the LS plays a key role in helping to filter and convert raw information about location, speed and acceleration coming in from regions such as the hippocampus, into more reward-specific output for regions known to guide goal-directed behavior.

Grant fuels effort to develop **Alzheimer's** drug

Recent studies suggest that misregulation of gene expression in the brain's innate immune cells, called microglia, may contribute to the progression of Alzheimer's disease. With a new grant from the National Institute on Aging, three member labs of The Neuroedgeneration Consortium (NDC) will collaborate to develop a drug that can inhibit a likely source of the misregulation, potentially delaying the onset of Alzheimer's symptoms.

"Our goal is to target a protein that regulates gene expression in microglia by developing a novel, small molecule compound to the point where it will be ready for phase I clinical trials," said Li-Huei Tsai, Picower Institute director and primary investigator on the grant, which will support the effort with up to $8 million over the next five years.

Tsai's lab will collaborate with those of NDC director William J. Ray, director of the drug discovery program at The University of Texas MD Anderson Cancer Center, and fellow NDC member Alison Goate, director of Ronald M. Loeb Center on Alzheimer's disease at Icahn School of Medicine at Mount Sinai.

In a paper in 2015 Tsai and MIT Computer Science Professor Manolis Kellis identified the protein PU.1 as a transcription factor responsible for regulating the expression of genes in microglia that were misregulated in Alzheimer's model mice and human patients. In 2017 Goate led a study showing that people with a genetic variation that reduced expression of the gene that encodes PU.1 had a significantly lower risk of developing Alzheimer's and did so at later age.

The NDC collaborators, including Ray's drug development team, have been pursuing the hypothesis that finding a drug that can inhibit PU.1 activity can delay the onset of Alzheimer's. After an extensive screening led by Tsai lab postdoc William Ralvenius, they have identified a compound with strong and specific effects in reducing PU.1 activity and modulating the expression of the same genes that PU.1 is responsible for regulating.

The team is working to refine the compound further. Ultimately the team's hope is that it will essentially mimic the effect of the Alzheimer's protective genetic variation Goate identified, thereby delaying the onset of Alzheimer's in patients.

"Even a few years delay in the age of Alzheimer's onset would provide tremendous benefit to millions of people, their caregivers and families and healthcare systems worldwide," the team's grant proposal states.

Grants '**Skyrocket**' research by investing in young scientists

National Institutes of Health "K99" grants not only help postdocs launch new research but also help them to pursue it further as independent scientists. The competitive grants are an honor – one that six Picower Institute postdocs have earned in the past four years out of 23 total awarded at MIT.

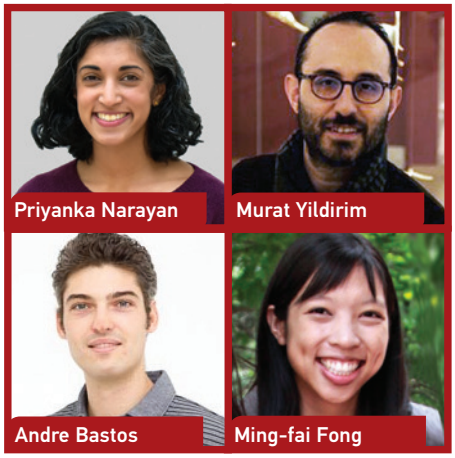
In April **PRIYANKA NARAYAN** moved from Cambridge to Bethesda, Md., to continue the Alzheimer's research program she conducted in the lab of Picower director Li-Huei Tsai in her own lab as a tenure-track investigator at the NIH.

When Narayan first started at MIT she studied the molecular and cellular effects of gene variants that increase Alzheimer's disease risk, like APOE4, by engineering them into yeast. With the K99 award she expanded her research skills and horizons, testing hypotheses from her yeast screens in human brain cell cultures derived from stem cells.

K99s provide postdocs with two years of funding to build skills and develop a career plan to launch a research program they can advance in their own lab at a new institution. When they successfully complete their postdoc, they earn the next-stage grant, an R00, for their first three years of their new position.

"The K99 funds two years of your postdoc to do something that will really skyrocket your research to a new and different place," Narayan said.

Picower's newest recipient is **MURAT YILDIRIM**, a postdoc in Mriganka Sur's lab. A microscope engineer, Yildirim came to MIT to build better imaging technology and apply it to neuroscience. With the K99, he studies how multiple regions of the brain connect and communicate to enable short-term memory. To advance those studies he built a "three-photon microscope" that can image neural activity deep within the brain. He combines its measurements with those from conventional two-photon scopes across multiple brain regions. He is also applying optogenetics, a technology that makes neurons controllable with flashes of visual light, to directly manipulate circuits.



In Picower Professor Earl Miller's lab, **ANDRE BASTOS** earned a K99 in 2018. Bastos studies higher-level cognition and is interested in how ensembles of neurons in multiple layers and regions of the cortex form expectations and carry out predictions about the environment. The brain must constantly evaluate whether incoming sensory information, like something it sees, is surprising or the same old thing and therefore, perhaps less important to investigate. Next summer Bastos will join the psychology department at Vanderbilt University establishing a lab focused on cognition, computation and consciousness.

K99 recipient **MING-FAI FONG**, a postdoc in the lab of Mark Bear, studies how the brain's ability to remodel and reconfigure circuits can help people improve their sensory abilities. An example has been developing a therapeutic strategy for amblyopia, a developmental visual disorder in which children with an impairment in one eye can lose acuity permanently as neural connections supporting vision there become repurposed to serve the stronger eye. Fong has shown that if the original visual impairment is corrected and the visual system is temporarily shut down, the brain essentially reboots and restores neural connections to support the formerly weaker eye, improving vision.

"This K99-R00 project has been a great way to leverage the Bear lab's expertise on experience-dependent visual cortical plasticity to explore interventional strategies for restoring or enhancing visual ability," Fong said.

Other recent Picower K99 recipients include Rafiq Huda, now at Rutgers, and Cody Siciliano, now at Vanderbilt. For them, too, the award not only launched new research, but also is supporting the people who carry it forward.

TOWARD GREATER DIVERSITY, EQUITY AND INCLUSION

Like much of MIT and the nation, the Building 46 community was anguished by the killing of George Floyd and moved by the protest and social action movement that followed. Brain and Cognitive Sciences graduate students led the call for a communitywide response, in which the leadership of the Picower Institute, the McGovern Institute, the Department of Brain and Cognitive Sciences, other building faculty, postdocs, and staff joined in standing against anti-Black racism and began collaborating on actions and commitments to recognize, understand, and address systemic racism in our own community and society at large. In June the community announced the following commitments:

*Expand the BCS Diversity Committee, adding new faculty members and to now include staff, postdoc, and graduate student members. Picower faculty members Myriam Heiman and Steve Flavell joined as did graduate students Hector De Jesus Cortez (Bear lab) and Lupe Cruz (Sur Lab).

*Contribute and raise funds dedicated to building an infrastructure that can enable lasting change.

*Use a portion of these funds to support anti-racist initiatives suggested by BCS graduate students.

*Use a portion of these funds to build relationships with Historically Black Colleges and other minority serving institutions with an eye toward supporting their work and offering faculty/student exchanges.

*Use a portion of these funds for outreach to local community colleges, state schools, and high schools to offer internship opportunities and expand our efforts to impact the pipeline.

*Use a portion of these funds to expand ongoing BCS efforts including the post-baccalaureate program, IAP workshops, and summer research immersion programs.

*Designate faculty members who can serve as points of first contact to allow for rapid responses to questions/concerns about racism in the department.

*Answer questions from any member of the community about diversity, equity, and inclusion with as much transparency and data as possible.

For more on diversity, equity and inclusion at the Picower Institute visit https://picower.mit.edu/about/diversity-equity-inclusion

From Biological Intelligence To artificial Intelligence

How Picower neuroscience research has mattered to AI

Basic discoveries about the brain by Institute faculty have contributed to efforts to develop intelligent machines, an analysis of citations shows

The daily business of Picower Institute professors is exploring the basic neuroscience of how the brain learns and remembers, but by virtue of that work, several of them have produced research over the last three decades that has mattered demonstrably to advances in the Artificial Intelligence field. Both when they have explicitly explored intersections with AI research and even when they haven't, their findings have provided inspiration, ideas and instruction to those questing to build smart machines.

Matthew Wilson's curiosity about the nature of intelligence, both biological and synthetic, dates back to his days as an electrical engineering student, but when it came time to choose a research direction, he dedicated himself to studying how large groups of neurons in the hippocampus and other brain regions represent, process, and employ memory in behavior. His discoveries including that animals replay memories of their daily activities when they sleep, that they also rehash them during rest while awake and that they even sometimes replay them backwards to retrace their steps have proven of substantial interest to AI researchers.

Last year, for example, when Matt Botvinick, head of neuroscience at the AI company DeepMind spoke at a conference at MIT, he specifically highlighted the Wilson lab's work, including a particular *Neuron* paper on replay, as having a direct influence on how programmers have designed algorithms to learn from past performance. Much as it does in animals, replay helps algorithms recursively identify and reinforce what went right and what went wrong – a concept called "deep reinforcement learning."

A couple of months after Botvinick made those remarks, DeepMind researchers co-authored a paper in *Cell* providing evidence that humans, too, use replay to refine and apply learning. The study not only cited four of Wilson's papers but also three by Susumu Tonegawa, who has shown that heading into an experience, rodents will also prepare by imagining what is to come, a phenomenon dubbed "preplay."

Indeed, citation of Picower faculty papers by studies having to do with AI is not rare. According to data from the Web of Science furnished by the MIT Libraries, through February 2020 more than 1,680 papers tagged as relevant to AI research have cited more than 200 papers authored by current Picower Institute faculty members – particularly those whose studies involve systems-level neuroscience like Wilson, Tonegawa, Earl Miller, Emery N. Brown, Mriganka Sur, and Mark Bear. The numbers don't shed any light on how much Picower faculty have influenced AI compared to others, but they do demonstrate that their work has mattered to the field.

The tallies also show *how* Picower research has mattered to AI by highlighting clear themes. Among the 25 Picower papers most cited by AI-related papers, several concern Wilson's studies of how the hippocampus and other regions encode motion through an environment, like a maze, and replay those memories. Another cluster of papers represent some of Miller's efforts to understand how the prefrontal cortex governs cognitive functions like working memory and selective attention. A few, including the most cited of all, derive from Sur's work to understand how the brain rewires itself based on experience to tune mental function to the demands of the world. And many highly-cited papers demonstrate that Brown's rigorous statistical methods for finding meaningful patterns in neural activity have been valuable for engineers who seek to represent that in algorithmic code.


Matthew Wilson

"A lot of the big ideas in AI were really derived from the biology, from neuroscience," observes Wilson, whose lab continues to explore how the hippocampus and connected regions encode context, reward and action to produce goal-directed behavior. "Basic science can provide the kind of novel insight that can fuel the next wave of innovation."

The ways in which Picower's fundamental research has fed into AI may become of heightened interest as MIT launches and builds its

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new Schwarzman College of Computing, which has a strong AI focus. "Ensuring that the future of computing is shaped by insights from other disciplines" is an explicit part of its mission.


Emery Brown

When Brown began his neuroscience research by collaborating with Wilson in the late 1990s, he did not anticipate the AI-relevance of his work. He was focused on developing mathematically principled statistical methods for more accurately decoding the neural activity of rats as they scampered through mazes and marked where they were. In a highly-cited *Journal of Neuroscience* paper with Wilson in 1998, for example, he showed that his methods reduced the error of estimating position based on neural activity from 30 centimeters to 8.

Brown's many advances in decoding patterns of motion from neural signals caught the attention of the brain-computer interface field, in which engineers have sought to create prosthetics by reading out the brain's thoughts of moving a missing or paralyzed arm, feeding those to a computer, and having the computer translate those thoughts into commands to move a cursor or a robotic arm. For this application of AI to truly help patients, it must be as accurate and quick as possible, which is why the field has cited Brown's work.

"We have to do algorithmic research to make sure it's optimal," Brown says.

Brown is not only a neuroscientist and statistician but also he is an anesthesiologist at Massachusetts General Hospital. In more recent work, his lab has developed statistical methods for accurately extracting meaningful patterns in EEG measurements of brain waves from patients under general anesthesia. The lab has shown, for instance, how the waves differ in older vs. younger patients, and how they are affected by different anesthetic drugs and their doses. He's implementing this knowledge in an AI-powered brain-computer interface of his own—one that will constantly monitor patient EEG readings to help anesthesiologists control dosing so patients can stay properly anesthetized without getting more drugs than needed.

Neither Brown nor Wilson call themselves AI researchers, of course, but they both maintain a formalized connection to the field via their affiliations with MIT's Center for Brains Minds and Machines, a National Science Foundation-funded entity that facilitates dialogue and collaboration among researchers who study different manifestations of intelligence – real and engineered.

Sur, too, has sometimes collaborated with AI-minded colleagues. Two decades ago he showed that the brain of a developing ferret was so adaptable that if the auditory cortex were cut off from input, it would instead rewire to help process visual input. The findings so intrigued colleagues in robotics, that he was invited to participate in a conference inspired by the vision that if robots were designed to build their intelligence based on the flexibility of the developing biological brain – i.e. to mimic the brain's "plasticity" to rewire neural connections based on experience – they might efficiently develop a flexible and general, rather than task-specific, intellect.

"The brain wires itself to process the world," Sur said.

Out of that meeting Sur co-authored a 2001 paper in *Science* describing this vision of "autonomous mental development" that has been cited by about 200 AI-related papers, according to the Web of Science.


Mriganka Sur

Sur has continued to study developmental plasticity in the brain and to understand the mechanisms of learning and action – including the role of non-neural cells such as astrocytes. Out of that, this summer he has found a new opportunity to interact with the AI field. With colleagues in MIT's Computer Science and Artificial Intelligence Lab he proposes to study a mechanism that might underlie the brain's capacity to learn even when a good or bad outcome arises only after several steps have occurred over significant time. Their hypothesis is that the slow but sustained activity of astrocytes might integrate many inputs over time to help circuits recognize these multi-step cause and effect relationships.

Miller says that although his work addresses many questions of how intelligent behavior emerges in the brain from the coordination of different regions and networks, he hasn't explicitly focused on connecting those findings with AI research. Nonetheless his work has been cited by AI-related researchers looking for inspiration from the natural operation of brain. For example, a 2001 review paper Miller co-authored on how the prefrontal cortex biases the function of other regions to ensure that activity is coordinated to achieve goals is the second most AI-cited Picower paper, according to the database, for instance by programmers considering algorithmic decision making or more basic issues of robotic control. Also among the top papers was one published in *Science* in 2007 that produced an explanation of volitional control over attention vs. more reflexive attention: Volition is synchronized with lower frequency brain waves emanating from the prefrontal cortex, while more reflexive attention (guided by the senses), depends on higher-frequency waves from sensory cortices. Miller continues to explore how other cognitive functions like working memory are also implemented by cortical networks.


Earl Miller

And like many of his colleagues, Miller is no stranger to computation. He maintains many collaborations with computational neuroscientists whose software models of brain function help him analyze experimental data. The ability of computing to enhance neuroscience, not just the ability of neuroscience to enhance computing, is also woven in the new College of Computing's DNA.

By serendipity, the College's new building, scheduled to open in 2023, will be built on Vassar Street right next to Building 46. That could lay the literal groundwork for new collaborations.

"My goal is to figure out the brain and their goal is to create a smart computer," Miller said. "If they see their pathway to making a smart computer by going through the biology of the brain, then they couldn't pick a better place to land their building next to. What we are doing is highly relevant if you are interested in how the brain produces intelligence."

Editor's note: To see the top 25 Picower faculty papers most cited by publications tagged as AI-related by the Web of Science, visit http://picower.mit.edu/news/AI-papers. We thank MIT Librarian Courtney Crummett for her help with the data.

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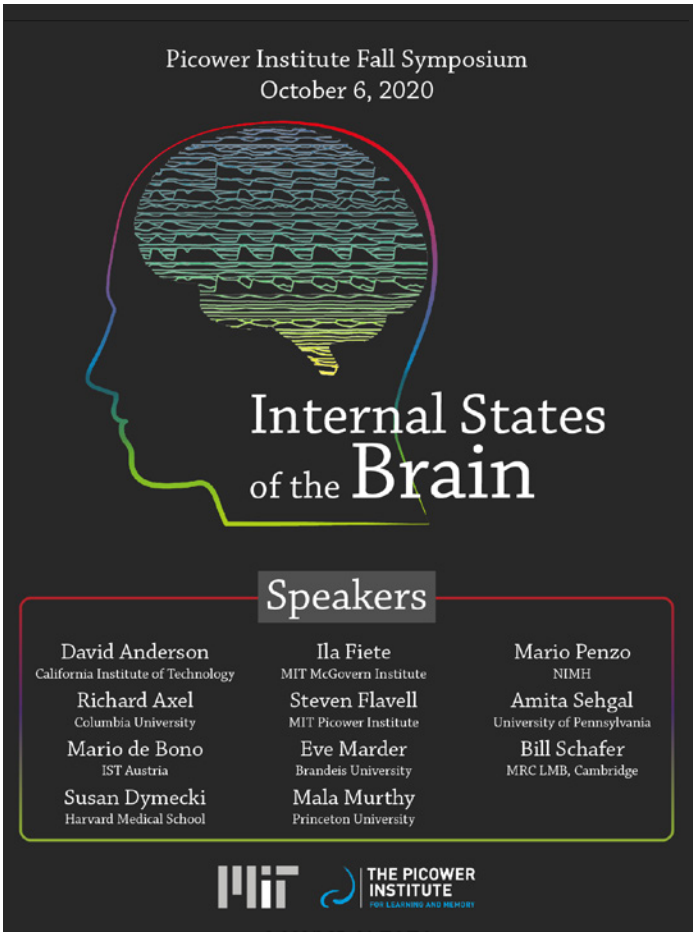
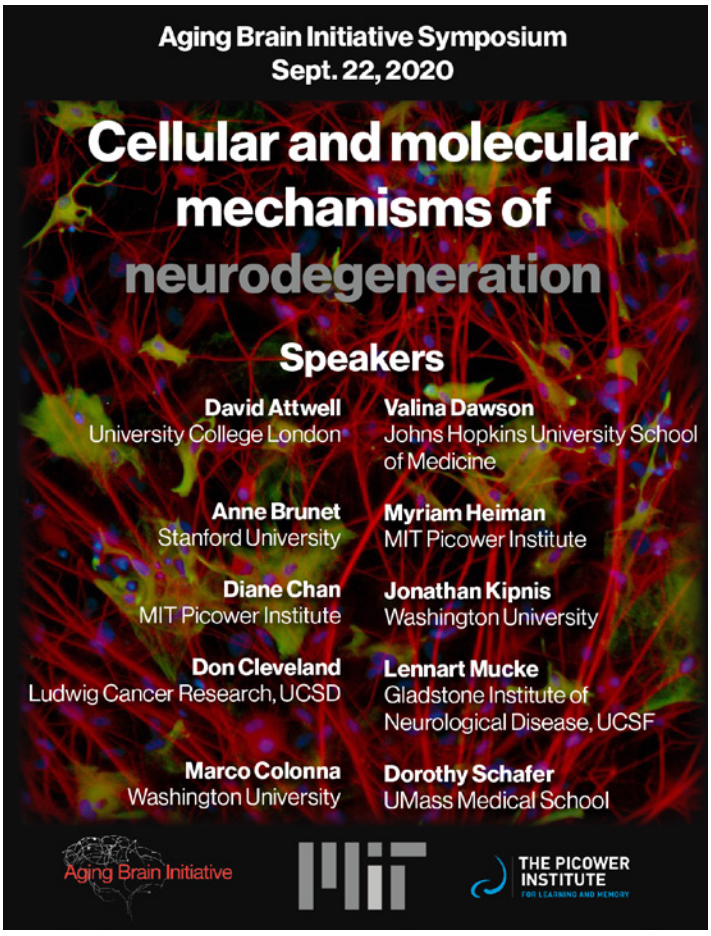
For the *latest* information on all our lectures, symposia and other events, please visit: **picower.mit.edu/events**

Upcoming Seminars and Colloquia

Due to the Covid-19 Pandemic our expectation is to hold these events via livestream . Please check the web address listed above for the latest information about these events and the rest of our fall schedule. Thank you for your understanding.





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The Picower Institute is a community of scientists dedicated to understanding the mechanisms that drive learning and memory and related functions such as cognition, emotion, perception, and consciousness. Institute researchers explore the brain at multiple scales, from genes and molecules, to cells and synapses, to circuits and systems, producing novel insights into how disruptions in these mechanisms can lead to developmental, psychiatric, or neurodegenerative disease.

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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