INSIDE

Focus on Fats

A Picower Institute lab is on a mission to discover how cells mishandle lipid molecules in Alzheimer's disease and is using that knowledge to develop treatments. Pg. 9

Neuroscience News

WINTER 2025

THE PICOWER INSTITUTE FOR LEARNING AND MEMORY

DIRECTOR'S **MESSAGE**

Dear Friends,

At The Picower Institute, we strive to understand how the brain works and we work to apply that knowledge to better understand and treat disease. You can see that whole continuum–from discovery to delivery–represented across the stories throughout this edition.

We report on many fundamental findings. Earl Miller's lab shows how brain waves help us track and remember what we see (p. 2 & p.4). Mriganka Sur's lab demonstrates a role in brain development for loop-shaped circular RNAs (p.5). Troy Littleton's lab reveals how neural activity shapes circuit connections (p.5). Even in these fundamental studies, clinical considerations are never far from mind. As Troy explains, understanding how circuit connections are built and work enables us to think about how to intervene if they don't work properly.

My lab, which seeks to understand neurological disorders such as Alzheimer's, has several stories in this edition that also span fundamental science and clinical considerations. We debut a sophisticated new human brain model that can be used for both basic research and personalized drug discovery (p.3), and we report on long-term results from a small panel of volunteers who've received 40Hz sensory stimulation to potentially treat Alzheimer's (p.4).

Our cover story (p.9), features years of research in our lab in which we've come to understand how lipid molecules, which have crucial roles throughout the brain, become misregulated in Alzheimer's. Our studies have delved deep into the basic biology of the relevant genes and pathways involved, but importantly with each study we've also found interventions to correct what goes awry.

Still, what works in the lab doesn't always work in the clinic. To increase the odds, we have launched a "derisking" initiative, seeded by the generous support of Kathy and Miguel Octavio (p.8). We're grateful and excited to launch this program to bring discovery closer to delivery.

Thank you for reading. All of us at The Picower Institute wish you a happy holiday season!

LI-HUEI TSAI, DIRECTOR

The Picower Institute for Learning and Memory

How the brain splits up **vision** without you even noticing

The brain divides vision between its two hemispheres—what's on your left is processed by your right hemisphere and vice versa—but your experience with every bike or bird that you see zipping by is seamless. A new study by Picower Institute neuroscientists reveals how the brain handles the transition.

"It's surprising to some people to hear that there's some independence between the hemispheres, because that doesn't really correspond to how we perceive reality," said Picower Professor Earl K. Miller. "In our consciousness, everything seems to be unified."

To conduct the study, published in the *Journal of Neuroscience*, the researchers measured both the electrical spiking of individual neurons and the various frequencies of brain waves that emerge from the coordinated activity of many neurons. They studied the dorsal and ventrolateral prefrontal cortex in both hemispheres, brain areas associated with executive brain functions.

The results showed that after the sending hemisphere initially encoded the target with a ventrolateral interplay of relatively higher frequency beta and gamma waves, a dorsolateral

The brain's hemispheres hand off vision like relay racers hand off a baton

There are advantages to separately processing vision on either side of the brain, including the ability to keep track of more things at once, Miller and other researchers have found, but neuroscientists have been eager to fully understand how perception ultimately appears so unified in the end.

Led by postdoctoral Picower Fellow Matthew Broschard and Research Scientist Jefferson Roy, the team measured neural activity in the brains of animals as they tracked objects crossing their field of view. The results reveal that different frequencies of brain waves encoded and then transferred information from one hemisphere to the other in advance of the crossing, and then held on to the object representation in both hemispheres until after the crossing was complete. The process is analogous to how relay racers hand off a baton, how a child swings from one monkey bar to the next, and how cell phone towers hand off a call from one to the next as a train passenger travels through their area. In all cases, the towers or hands actively hold what's being transferred until the handoff is confirmed.

ramp up of slower alpha waves caused the receiving hemisphere to anticipate the handoff by mirroring the sending hemisphere's encoding of the target information. Alpha peaked just after the target crossed the middle of the field of view, and when the handoff was complete, slower theta waves peaked in the receiving hemisphere as if to say, "I got it."

The study shows that the brain is not simply tracking objects in one hemisphere and then just picking them up anew when they enter the field of view of the other hemisphere.

"These results suggest there are active mechanisms that transfer information between cerebral hemispheres," the authors wrote. "The brain seems to anticipate the transfer and acknowledge its completion."

But they also note based on other studies that the system of interhemispheric coordination can sometimes appear to break down in certain neurological conditions including schizophrenia, autism, depression, dyslexia and multiple sclerosis. The new study may lend insight into the specific dynamics needed for it to succeed.

MIT invents human brain model with all six major cell types

A new 3D human brain tissue platform is the first to integrate all major brain cell types, including neurons, glial cells and the vasculature in a single culture. Grown from individual donors' induced pluripotent stem cells, these models—dubbed Multicellular Integrated Brains (miBrains)—replicate key features and functions of human brain tissue, are readily customizable through gene editing, and can be produced in quantities that support large-scale research.

Although each unit is smaller than a dime, miBrains may be worth a great deal to researchers and drug developers who need more complex living lab models to better understand brain biology and treat diseases.

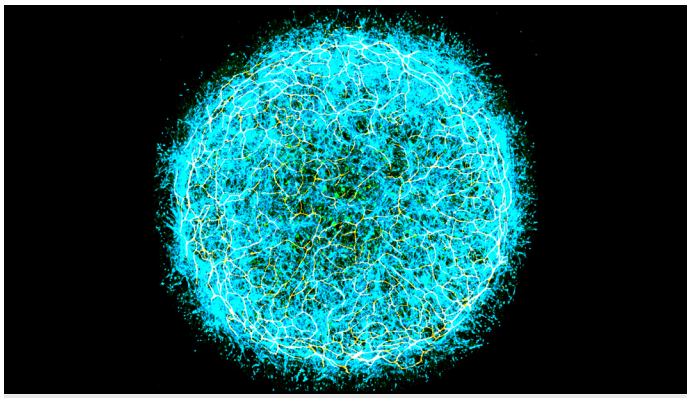
"I'm most excited by the possibility to create individualized miBrains for different patients," said Picower Professor Li-Huei Tsai. "This promises to pave the way for developing personalized medicine."

Tsai's co-senior authors are Robert Langer, David H. Koch (1962) Institute Professor, and Joel Blanchard, associate professor in the Icahn School of Medicine at Mt. Sinai in New York and a former Tsai Laboratory postdoc. The study is led by Alice Stanton and Adele Bubnys.

Simpler cultures of just one or a few cell types can be created in quantity relatively easily and quickly, but they cannot tell researchers about the myriad interactions that are essential to understanding health or disease. Animal models embody the brain's complexity, but can be difficult and expensive to maintain, slow to yield results, and different enough from humans to yield occasionally divergent results.

miBrains combine advantages from each type of model, retaining much of the accessibility and speed of lab-cultured cell lines while allowing researchers to obtain results that more closely reflect the complex biology of human brain tissue. Moreover, they are derived from individual patients making them personalized to an individual's genome. In the model, the six cell types self-assemble into functioning units, including blood vessels, immune defenses, and nerve signal conduction, among other features. Researchers ensured that miBrains also possess a blood-brain-barrier capable of gatekeeping which substances may enter the brain, including most traditional drugs.

To test miBrain's capabilities, the researchers embarked on a study of the gene variant APOE4, which is the strongest genetic predictor for the development of Alzheimer's disease. The researchers tracked the Alzheimer's-associated proteins amyloid and phosphorylated tau, and found all-APOE4 miBrains accumulated them, whereas all-APOE3 miBrains did not. However, in APOE3 miBrains with APOE4 astrocytes, they found that miBrains still exhibited amyloid and tau accumulation. Moreover, they found that astrocytes needed microglia cells to generate the pathology.



miBrains integrate multiple brain cell types.

Rare gene variant contributes to Alzheimer's disease

A new study from MIT neuroscientists reveals how rare variants of a gene called ABCA7 may contribute to the development of Alzheimer's in some of the people who carry it. The mutations can disrupt the metabolism of lipids that play an important role in cell membranes.

This disruption makes neurons hyperexcitable and leads them into a stressed state that can damage DNA and other cellular components. These effects, the researchers found, could be reversed by treating neurons with CDP-choline, an important building block precursor needed to make cell membranes.

"We found pretty strikingly that when we treated these cells with choline, a lot of the transcriptional defects were reversed. We also found that the hyperexcitability phenotype and elevated amyloid beta peptides that we observed in neurons that lost ABCA7 was reduced after treatment," said lead author Djuna von Maydell, a postdoc and former graduate student.

Picower Professor Li-Huei Tsai, director of The Picower Institute is the senior author of the paper in *Nature*.

ABCA7 encodes a protein that transports lipids across cell membranes. To explore how ABCA7 variants might contribute to Alzheimer's risk, the researchers obtained human tissue samples from carriers. They found that the most significantly affected genes fell into clusters related to lipid metabolism, DNA damage, and oxidative phosphorylation (the metabolic process that cells use to capture energy as ATP).

To investigate how those alterations could affect neuron function, the researchers introduced ABCA7 variants into neurons derived from induced pluripotent stem cells.

Using these engineered cells, the researchers analyzed the effects of ABCA7 variants on lipid metabolism. The variants altered metabolism of a molecule called phosphatidylcholine, which could lead to membrane stiffness and may explain why mitochondrial membranes of the cells were unable to function normally. Those findings raised the possibility that intervening in phosphatidylcholine metabolism might reverse some of the cellular effects of ABCA7 loss. To test that idea, the researchers treated neurons with ABCA7 mutations with CDP-choline.

Like radar, a brain wave sweeps a cortical region for **working memory**

To spot a crime, security guards who sit at banks of security monitors must recognize changes in what they're seeing. That's a visual working memory challenge. According to Picower Institute scientists, the ability to quickly spot visual changes could depend on a theta frequency brain wave (3-6 Hz) that scans through a region of the cortex that maps one's field of view.

The findings in animals, published in *Neuron*, help to explain how the brain implements visual working memory and why performance is both limited and variable.

"This shows that waves impact performance as they sweep across the surface of cortex. This raises the possibility that traveling waves are organizing or even performing neural computation," said Picower Professor Earl K. Miller, senior author of the study. Hio-Been Han is the lead author.

In the study, animals played a video game in which an array of colored squares appeared and then disappeared on a screen. After about a second, the array reappeared with one square sporting a different color. The animals had to glance at the one that changed, ideally as quickly as possible. To keep score, the researchers tracked the reaction time and position of the animals' gaze. They also measured brain wave power across a broad frequency spectrum and individual neural electrical "spikes" in a region called the "frontal eye fields" that maps visual information analogously to the where it first hits the retina (a "retinotopic" map).

The researchers noticed that the animals' accuracy and speed turned out to depend on a combination of the phase of a theta frequency brainwave when the changed square appeared, and the vertical location on the screen of that target square. In other words, each height on the screen had its own phase of the theta wave where performance was at its best, and the lower a target square appeared on the screen, the later the phase of the wave that correlated with peak performance.

"The optimal theta phase for behavior varied by retinotopic target location, progressing from the top to the bottom of the visual field," the researchers wrote in *Neuron*. "This could be explained by a traveling wave of activity across the cortical surface during the memory delay."

40Hz sensory stimulation may benefit some **Alzheimer's** patients for years

A new research paper documents the outcomes of five volunteers who continued to receive 40Hz light and sound stimulation for around two years after participating in an MIT early-stage clinical study of the potential Alzheimer's disease therapy. The results show that for the three participants with late-onset Alzheimer's disease, several measures of cognition remained significantly higher than comparable Alzheimer's patients in national databases. Moreover, in the two late-onset volunteers who donated plasma samples, levels of Alzheimer's biomarker tau proteins were significantly decreased.

Two other participants, each of whom had early-onset forms of the disease, did not exhibit significant benefits after two years. The dataset, while small, represents the longest-term test so far of the safe, non-invasive treatment method (called GENUS, for gamma entrainment using sensory stimuli), which is also being evaluated in a nationwide clinical trial run by MIT-spinoff company Cognito Therapeutics.

"This pilot study assessed the long-term effects of daily 40Hz multimodal GENUS in patients with mild AD," the authors wrote in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*. "We found that daily 40Hz audiovisual stimulation over 2 years is safe, feasible, and may slow cognitive decline and biomarker progression, especially in late-onset AD patients."

Diane Chan is the study's lead and co-corresponding author. Picower Professor Li-Huei Tsai, director of The Picower Institute and the Aging Brain Initiative at MIT, is the study's senior and co-corresponding author.

In 2020, MIT enrolled 15 volunteers with mild Alzheimer's disease in an early-stage trial to evaluate whether an hour a day of 40Hz light and sound stimulation, delivered via an LED panel and speaker in their homes, could deliver clinically meaningful benefits. Indeed volunteers experienced some at the three-month mark.

Five volunteers came back to MIT for a series of tests 30 months after their initial enrollment. The three late-onset Alzheimer's volunteers showed improvement or slower decline on several cognitive tests, including significantly positive differences compared to controls on three of them. These volunteers also showed increased brain-wave responsiveness to the stimulation at 30 months and showed improvement in measures of circadian rhythms. In the two late-onset volunteers who gave blood samples, there were significant declines in phosphorylated tau (47 percent for one and 19.4 percent for the other) on a test recently approved by the FDA as the first plasma biomarker for diagnosing Alzheimer's.

Neural activity helps circuit connections mature

Nervous system functions from motion to perception to cognition depend on the active zones of neural circuit connections, or "synapses," sending out the right amount of their chemical signals at the right times. By tracking how synaptic active zones form and mature in fruit flies, researchers in The Picower Institute have revealed a fundamental model for how neural activity during development builds properly working connections.

Understanding how that happens is important, not only for advancing fundamental knowledge about how nervous systems develop, but also because many disorders such as epilepsy, autism, or intellectual disability can arise from aberrations of synaptic transmission, said Menicon Professor Troy Littleton, the study's senior author.

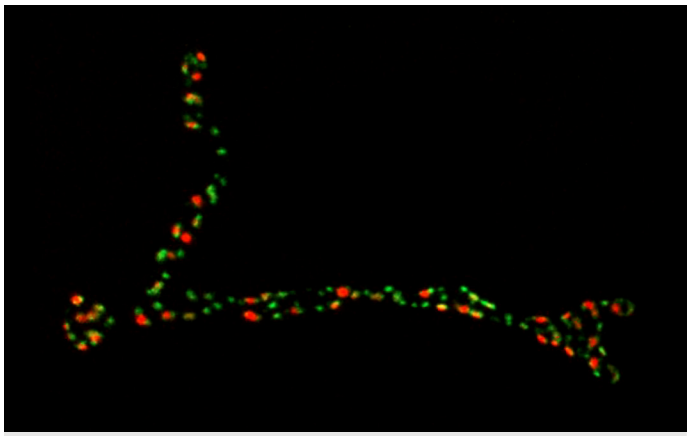
If scientists can fully understand the process, Littleton said, then they can develop molecular strategies to tweak synaptic transmission when it's happening too much or too little in disease.

"We'd like to have the levers to push to make synapses stronger or weaker," Littleton said. "And so knowing the full range of levers we can tug on to potentially change output would be exciting."

Littleton Lab research scientist Yuliya Akbergenova led the study published in the *Journal of Neuroscience*.

In the study, the researchers examined neurons that send the neurotransmitter glutamate across synapses to control muscles in fly larvae. To study how the active zones in the animals matured, the scientists needed to keep track of their age. That hasn't been possible before, but Akbergenova overcame the barrier.

With the ability to track each active zone's birthday, the authors could then document how active zones developed their ability to increase output over the course of days after birth. The researchers actually watched as synapses were built over many hours by tagging each of eight kinds of proteins that make up an active zone.



Fluorescence along a segment of a neural axon indicates time-stamped synapses. *Image by Yulia Akbergenova*

Normally, as active zones mature, the fly larva stops building one synapse and then builds new ones further down the line as the neuronal axon expands to keep up with growing muscles. The researchers wondered whether the neural activity of neurotransmitter release had a role in marking the moment, so they blocked it to see what would happen. They observed two consequences: the neurons stopped building new active zones and instead kept making existing active zones larger and larger, as if to compensate for the lack of activity. Thus, activity proved to be a key cue for when an active zone was mature.

Circular RNA helps drive brain development

A huge crew of molecules wires up the brain's trillions of circuit connections. Among the less understood members are circular RNAs, transcripts from DNA that assume a closed loop shape. A new study shows that one such circular RNA from the Homer gene, "*circHomer1*," takes on a significant and somewhat surprising role in how the developing brains of mice formed connections, or "synapses," in the visual system.

In the study, the team demonstrates that interfering with *circHomer1* not only undermined the normal development of synapses, but also delayed visual system neurons from making the expected adjustments when the scientists performed a classic experiment of temporarily blocking vision through one eye, a protocol called "monocular deprivation" (MD).

"It is used to build synapses, for sure." said co-senior author Mriganka Sur, Newton Professor in The Picower Institute. "When you knock it down, the synapses, at least structurally, are not fully built. Then, after monocular deprivation, when the dendritic spines housing synapses normally should shrink, as should responses from the blocked eye, knocking down *circHomer1* prevented that for three days."

The lead authors of the study published in *iScience* are Sur Lab postdoc Kyle Jenks, former MIT graduate student Marvin Nayan, and graduate student Ying Cai in the lab of co-senior author and former Sur Lab postdoc Jacque Pak Kan Ip, at the Chinese University of Hong Kong.

Sur's lab has been curious about how different forms of RNA affect how synapses are built, particularly in response to nervous system activity (such as visual input) during development. The brain's ability to adjust its networks to accommodate activity, an attribute called "plasticity," is crucial to development, learning and memory.

The new study therefore began with an unbiased screen for RNAs, circular and linear, that showed significant differences in their degree of expression when the researchers performed the MD experiment. The screen showed that 73 circular RNAs were differentially expressed. What made *circHomer1* stand out in particular was that its expression increased for the first three days of MD even as the linear *Homer1a*'s expression decreased during that same time.

Intrigued, the team measured *circHomer1*'s expression levels during normal development and saw that it increases significantly at the start of the "critical period" when the brain undergoes a lot of remodeling to account for experience.

They also devised a way to knock it down. When they did, they saw that the brain's expected changes amid MD were delayed.

Symposium examines the neural circuits that keep us alive and well

Taking the audience on a tour around the body, seven speakers at The Picower Institute's symposium "Circuits of Survival and Homeostasis" Oct. 21 shared their newest research about some of the nervous system's most evolutionarily ancient functions.

Introducing the symposium she arranged with a picture of a man at a campfire on a frigid day, Assistant Professor Sara Prescott pointed out that the brain and the body cooperate constantly just to keep us going, and that when the systems they maintain fail, the consequence is disease.

"[This man] is tightly regulating his blood pressure, glucose levels, his energy expenditure, inflammation and breathing rate, and he's doing this in the face of a fluctuating external environment," Prescott said. "Behind each of these processes there are networks of neurons that are working quietly in the background to maintain internal stability. And this is, of course, the brain's oldest job."

Li Ye, a scientist at Scripps Research, picked right up on the example of coping with the cold. Mammals need to maintain a consistent internal body temperature, and so they will increase metabolism in the cold and then, as energy supplies dwindle, seek out more food. His lab's 2023 study identified the circuit, centered in the thalamus, that regulates this behavior by sensing prolonged cold exposure and energy consumption.

Physiologist Zachary Knight of UC San Francisco also studies feeding and drinking behaviors including how the brain knows when to stop. The conventional wisdom is that all that's needed is a feeling of fullness coming from the gut, but his research shows there is more to it. A 2023 study from his lab found a population of neurons in the brainstem that receive signals about ingestion and taste from the mouth, and that send that 'stop eating' signal. They've also found a separate neural population in the brainstem that indeed receives fullness signals from the gut, and teaches the brain over time how much food leads to satisfaction. Both neuron types work together to regulate the pace of eating.

When food is truly scarce, many animals will engage in a state of radically lowered metabolism called torpor (like hibernation), where body temperature plummets. In his talk, Harvard neurologist Clifford Saper described how his lab found neurons in the median preoptic nucleus that dictate this metabolic state. Recently, his lab demonstrated that the same neurons also regulate fever during sickness. When the neurons are active, body temperature drops. When they are inhibited, fever ensues. Thus, the same neurons act as a two-way switch for body temperature in response to different threatening conditions.

Washington University neuroscientist Qin Liu described her research into the circuits governing coughing and sneezing. She described her lab's 2024 study in which her team pinpointed a population of neurons in the nasal passages that mediate sneezing and a different population of sensory neurons in the trachea that produce coughing. Identifying the specific cells and their unique characteristics makes them potentially viable drug targets.

Harvard stem cell biologist Ya-Chieh Hsu discussed how neurons can reshape the body's tissues during stress and injury, specifically the hair and skin. In 2020 her team showed that bursts of noradrenaline from the hyperactivation of nerves in the sympathetic nervous system kills the melanocyte stem cells that give hair its color. Newer research indicates a similar mechanism may also make hair fall out by killing off cells at the base of hair follicles, releasing cellular debris and triggering auto-immunity. Meanwhile, though our skin may appear to heal after a cut because it closes up, many skin cell types don't rebound (unless you're still an embryo). By looking at the difference between embryos and post-birth mice, Hsu's lab has traced the neural mechanisms that prevent fuller healing.

Caltech biologist Yuki Oka discussed his lab's research to develop a molecular and cellular atlas of the sympathetic nervous system, which innervates much of the body and famously produces its "fight or flight" responses. In work partly published last year, their journey touched on cells and circuits involved in functions ranging from salivation to secreting bile.

Li Ye of Scripps Research delivers a talk on circuits that regulate the brain's feeding behavior.

In his talk, Stanford biochemist Mark Krasnow described how working with a new model organism, the mouse lemur, has led him to new insights into heart arrhythmias. After studying the genes and health of hundreds of mouse lemurs, his lab identified a family with "sick sinus syndrome," an arrhythmia also seen in humans. In a preprint study his lab describes the specific molecular pathways at fault in disrupting the heart's natural pacemaking.

By sharing some of the latest research into how the brain and body work to stay healthy, the symposium's speakers highlighted the most current thinking about the nervous system's most primal purposes.

Immune-informed brain aging research offers new treatment possibilities, speakers say

Understanding how interactions between the brain and the immune system contribute to problems of aging, including Alzheimer's, Parkinson's disease, arthritis and more, can generate new leads for therapeutic development, speakers said at MIT's symposium "The Neuro-Immune Axis and the Aging Brain" Sept 18.

Keynote speaker Michal Schwartz of the Weizmann Institute in Israel has found that an immune signaling cascade can arise with aging that undermines cognitive function. She has leveraged that insight to investigate and develop corrective immunotherapies that improve the brain's immune response to Alzheimer's both by rejuvenating the brain's microglia immune cells and bringing in the help of peripheral immune cells called macrophages.

In her presentation, Picower Professor Li-Huei Tsai, director of The Picower Institute and the Aging Brain Initiative, described recent collaborative work showing that many of the genes associated with Alzheimer's disease are most strongly expressed in microglia, giving it an expression profile similar to autoimmune disorders. The study showed that microglia become "exhausted" over the course of disease progression, losing their cellular identity and becoming harmfully inflammatory. Tsai said her lab is now also looking into how immune T cells, recruited by microglia, may also contribute to Alzheimer's progression.

Assistant Professor Sara Prescott delivers her talk. *Photo by Nina Thirakoune*

Several speakers focused on the vagus nerve, a major conduit between the brain and the body's major organs.

Picower Institute Assistant Professor Sara Prescott said the brain's communication via vagus nerve terminals in the body's airways is crucial for managing the body's defense of respiratory tissues. Our airways are exposed to many environmental challenges, Prescott noted, and her lab and others are finding that the nervous system interacts directly with immune pathways to mount physiological responses. But vagal reflexes decline in aging, increasing susceptibility to infection and so her lab is now working in mouse models to study airway-to-brain neurons throughout the lifespan.

Caltech Professor Sarkis Mazmanian focused on links between the gut microbiome and Parkinson's disease. His lab hypothesizes that the microbiome can nucleate the protein alpha-synuclein in the gut via a bacterial amyloid protein which may subsequently promote pathology in the brain, potentially via the vagus nerve. Based on its studies, the lab has developed two interventions: A high-fiber diet to increase short-chain fatty acids in the gut and a drug to disrupt the bacterial amyloid in the gut to prevent alpha-synuclein formation.

Kevin Tracey, Professor at Hofstra University and Northwell Health, took listeners to the spleen, describing how impulses in the vagus nerve regulate immune system emissions of signaling molecules, or "cytokines." Too great a surge can become harmful, for instance causing the autoimmune disorder rheumatoid arthritis. Tracey described a newly FDA-approved implant that stimulates the vagus nerve to help patients with severe forms of the disease.

Other speakers focused on the "borders" where the brain's and body's immune system meet.

Harvard Medical School Professor Beth Stevens of Boston Children's Hospital described a project where her lab found that "border-associated macrophages"— long-lived immune cells residing in the brain's borders — exhibited circadian rhythms in gene expression and function. Stevens said the cells are tuned by the circadian clock to "eat" more during the rest phase, a process which may help remove material draining from the brain, including Alzheimer's-associated peptides such as amyloid-beta. So, Stevens hypothesizes, circadian disruptions, for example due to aging or night-shift work, may contribute to disease onset by disrupting this immune-mediated "clean-up."

Washington University Professor Marco Colonna traced how macrophages, including border macrophages and microglia, develop via gene-expression programs that guide their differentiation into one type or another. One gene, for instance, is necessary for border macrophages along the brain's vasculature to help regulate the waste-clearing cerebrospinal flow (CSF) that Stevens also discussed. His lab has found that versions of the gene may be somewhat protective against Alzheimer's and that regulating expression of the gene could be a therapeutic strategy.

WashU's Jonathan Kipnis discussed macrophages associated with the border between brain tissue and the plumbing alongside the vasculature that carries CSF. The macrophages, his lab showed in 2022, actively govern the flow of CSF. Removing the macrophages let Alzheimer's proteins accumulate in mice. He's continuing to investigate how these border macrophages may play roles in disease and is looking at how the skull's brain marrow contributes to the population of immune cells in the brain and may play a role in neurodegeneration.

Harvard Medical School Professor Isaac Chiu focused on how neurons participate in their own immune defense, for instance by directly sensing pathogens and giving off inflammation signals upon cell death. He discussed a key molecule in that latter process, which is expressed among neurons all over the brain.

In many ways, speakers showed that age-related nervous system diseases are not only better understood but also possibly better treated by accounting for the immune system.

Impact of giving

Gift launches **'derisking'** initiative to accelerate development of promising discoveries

With seed funding from Kathy and Miguel Octavio, The Picower Institute is building a program to make basic discoveries more ready for commercial consideration.

After meeting at Clark University as undergraduates, Kathy and Miguel Octavio each earned PhDs (she at MIT and he at Harvard), but while Miguel's physics research focused on fundamental discovery, Kathy's engineering experience as an early employee of the research and technical support branch of Venezuela's state-owned oil company in the 1980s called for tackling practical problems. If her technical team needed to, say, find a new catalyst for the oil refining process, it wasn't a success unless it was used in production.

"The job isn't finished until it is doing something useful," Kathy Octavio said.

Kathy and Miguel Octavio on their 50th Anniversary.
Image courtesy of the Octavios

Now the couple faces a very different challenge. Years ago, Miguel experienced a terrible accident in which he suffered a traumatic brain injury that has since progressed to dementia. Kathy and aides work to keep his physical and cognitive abilities as sharp as they can. With their strong background in science and engineering, Octavio said she and her husband feel strongly that research provides the best chance to deliver the advances they and millions of others around the world need to treat dementia, and so for years they have supported the research of the Aging Brain Initiative and Picower Institute director Li-Huei Tsai. But with the practical spirit that infused her work in Venezuela, Octavio said that even the most promising lab research won't help if it never gets into the marketplace to reach the consumers who need it. That's why she and Miguel have provided the seed funding for a new initiative at The Picower Institute: A "derisking" program that will help Institute researchers advance testing of their discoveries in ways investors need before they'll be willing to bet on the costly process of turning them into therapies.

"If you don't do derisking, you don't get it out to the general public," said Octavio. Derisking is what brings discovery out of the lab to the kitchen table, she said.

When she first heard that Tsai was interested in derisking, Octavio was inspired to help. Tsai said the gift will not only get the program going, but also builds a foundation of support that contributions from other donors can build on to expand and sustain it.

"I'm so grateful Kathy and Miguel share our vision and are generously helping to make it real," Tsai said. "We are excited that work is getting underway and to imagine the impact this could have for patients and their families as others join in helping us grow it."

To lead the work, The Picower Institute has hired Zach Malchano, a biomedical engineer, entrepreneur and biotech executive whose work at Cognito Therapeutics has helped bring Tsai's 40Hz sensory stimulation technology to a national stage III clinical trial as a potential Alzheimer's disease therapy.

Malchano said that when a lab makes a discovery that's relevant to health, a key first step is to assess what the market need is and then work backward from there: What additional evidence would demonstrate the discovery's clinical value and viability? For instance, does an intervention that worked in a lab culture need to be tested in more sophisticated human cell culture, or with additional animal models? Do initial results from the lab need to be replicated at a greater scale? For the most promising projects, Malchano said, researchers can be connected with advisors to provide guidance through the process.

Another benefit of the program, Malchano said, is that postdocs, graduate students and other trainees involved in derisking work will have the chance to learn how discoveries become commercialized—a key set of skills if they are looking for careers in industry.

The initiative is headquartered in lab and office space the Institute recently leased and renovated at 730 Main St. in Cambridge, just a few blocks from Building 46, but Malchano said he is also exploring how commercial contract labs could provide an efficient way to amplify what can be done on campus.

After talking with faculty across the Institute, Malchano said he's found no shortage of ideas worth pursuing further, for instance in the labs of Professors Tsai, Mark Bear, and Sara Prescott.

Derisking isn't traditionally part of academic science, but aware of what families like the Octavios are going through, Picower scientists find strong motivation to see discovery through to making a medical difference. In turn, the Octavios' gift is enabling that.

"Just to watch your loved one go through that process of dementia can be heartbreaking," Octavio said. "I admire Li-Huei's work very much and what is coming out of it, so I would like to see it more widely available to people."

Focus on Fats

A Picower Institute lab is on a mission to discover how cells mishandle lipid molecules in Alzheimer's disease and is using that knowledge to develop treatments.

Some of us labor to drive down our body fat percentage, so it might feel shocking to learn that the brain is estimated to be 60 percent fat. But don't worry. The brain is fatty for good reason. Fats are essential for brain structure and function.

Various lipids compose the membranes of brain cells and form the vesicles that contain and transport the neurotransmitters that enable neuronal communication. To improve conduction of their electrical signals, most neurons insulate the long projections, or "axons," that extend from their cell bodies with sheaths of a substance called myelin that is rich in cholesterol. And the power plants of energy-hungry neurons, mitochondria, fuel themselves with fatty acid molecules.

But with great responsibility comes great vulnerability. If brain cells mishandle lipid molecules, disease can result. A rapidly growing evidence base shows that's exactly the case with Alzheimer's disease. Many important papers providing that evidence have come from the lab of Picower Professor and Picower Institute director Li-Huei Tsai. A major arm of her lab's research is dedicated to not only understanding the genetic, molecular and cellular basis for how lipid dysregulation drives Alzheimer's disease pathology and symptoms, but also to turning that knowledge into potential therapies.

Alois Alzheimer documented abnormal fatty deposits in brain cells, but he also saw other pathology (amyloid plaques and tau tangles) that have attracted most of the attention since. And while researchers have known for about 30 years that the APOE4 variation of the cholesterol transporting gene APOE is a huge risk factor, other genes have taken the limelight. But after looking at how APOE4 affects different brain cells in a study in 2018 in *Neuron*, Tsai's lab has published a series of research articles that have put lipids at the center of Alzheimer's pathology in every major kind of brain cell.

Importantly, in each study her lab has not only identified specific problems with lipid regulation, but has also been able to identify a remedy that sets them right again.

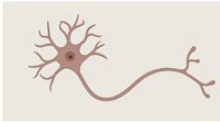
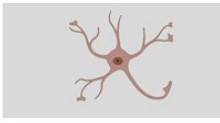
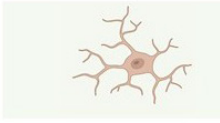
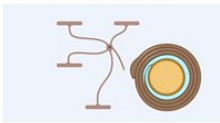
Neurons (red) in cell culture from a 2022 experiment where researchers showed that APOE4 microglia cells failed to support neuronal network communication. *Credit: Matheus Victor, Assistant Professor at Mount Sinai School of Medicine.*

"Once you normalize the lipid homeostasis in all these different cell types you can reduce pathology," Tsai said. "That strongly suggests that lipid dysregulation contributes to the pathophysiology."

Fats and failure: Cell by cell

About a quarter of people on the planet have at least one copy of the APOE4 variant (vs. the benign APOE3 version). One copy increases the risk of developing Alzheimer's by 3-fold, and having two copies increases it by more than 10-fold.

"We really are all in on APOE4," Tsai said. "My lab is trying to do everything it can to understand APOE4."

		Lipid-associated problems	What helps (in lab tests)
Neurons (ABCA7)		• Hyperexcitability • Increased amyloid secretion • Mitochondria defects	• Choline
Astrocytes (APOE4)		• Triglyceride accumulation • Decreased amyloid uptake	• Choline
Microglia (APOE4)		• Lipid accumulation • Pro-Inflammatory • Decreased amyloid, cholesterol uptake	• Triacsin C
Oligodendrocytes (APOE4)		• Cholesterol accumulation • Reduced myelination	• Cyclodextrin • Gsk3B inhibition

In that pioneering 2018 study, the lab took skin cells from donors and induced them to become stem cells. Then they turned those into three kinds of brain cells: neurons, microglia immune cells, and astrocytes. They edited some of the cells with CRISPR to make some of them carry APOE4, if they had APOE3, and vice versa. In each cell type they could see dramatic differences, including a big jump in cholesterol secretion by APOE4 astrocytes. Editing APOE4 cells to become APOE3 carriers corrected the problems, including the excess cholesterol in astrocytes.

In several more studies over the next few years, the lab followed up on each cell type and also in oligodendrocytes, cells that produce myelin. Because each kind of cell has different jobs in the brain, Tsai said, the lab has found that lipid dysregulation undermines their function differently.

(Continued on next page)

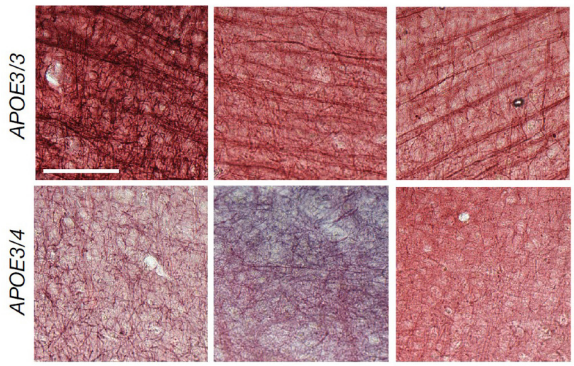
In 2021 in *Science Translational Medicine*, for example, the lab teamed up with that of the late Susan Lindquist at the Whitehead Institute to more deeply investigate astrocytes. Led by Grzegorz Sienski, Priyanka Narayan and Maeve Bonner, the team generated APOE3 and APOE4 versions of the cells and scrutinized their lipids. As before, the APOE4 astrocytes showed buildup of lipids including triglycerides, which were unusually rich in chains of unsaturated fatty acids. The researchers also profiled lipids and gene expression in yeast cells engineered to have APOE4. The analyses showed that APOE4 yeast experienced a growth defect because of the same kinds of lipid disruptions evident in astrocytes. But the scientists also found a way to reverse it. Cells use a process called the Kennedy Pathway to help build cell membranes with lipids, and this process depends on levels of a common nutrient called choline (we get it from sources such as eggs, meats, beans and nuts). In choline-deficient media, APOE3 got by but APOE4 yeast couldn't even survive. But with extra doses of choline APOE4 yeast could grow normally. The scientists found that APOE4 cells needed more choline than APOE3 cells did. Moreover, when they gave the yeast cells or the astrocytes extra choline, their lipid imbalances were resolved and the cells returned to healthier function.

The study also identified lipid dysregulation in microglia cells, but the Tsai lab's focus on those cells came the next year in a study in *Cell Stem Cell*. There, Matheus Victor led the lab in discovering that an unwelcome buildup of lipids in APOE4 microglia not only made them more inflammatory, but also compromised their ability to clean up cholesterol from the space they shared with neighboring neurons. That excess extracellular cholesterol turned out to disrupt the neurons' ability to regulate their electrical excitation, which is key to their ability to communicate in brain circuits. But much like they found that choline could rescue APOE4 astrocytes, the team found in their cell cultures that the lipid droplet reducing drug Triacsin C rescued APOE4 microglia function and the electrical activity of their neural neighbors.

Later that year in *Nature*, Joel Blanchard, Leyla Akay and Djuna von Maydell led the lab in a study that looked at gene expression and lipidomic differences across different cell types in human brains with APOE4 vs. APOE3. They confirmed major differences in how cholesterol is handled in cells. APOE4 oligodendrocytes showed profound increases in cholesterol biosynthesis yet decreases in expression of myelination genes. They accumulated cholesterol within their cell bodies and failed to deploy it as myelin around neurons. Looking in post-mortem brain samples of APOE4-carrying people with Alzheimer's the researchers saw significant deficits in myelination. But when they added the drug cyclodextrin, which facilitates cholesterol transport, APOE4 oligodendrocytes improved their myelination of neurons in co-culture. And in mice with APOE4, cyclodextrin improved myelination, learning and memory.

The studies have continued into this year. In a new preprint posted online, Akay dug deeper into how APOE4 oligodendrocytes over-accumulate lipids and discovered that hyperactivation of an enzyme called GSK3b is a linchpin. Inhibiting its activity, the team shows, reduces lipid droplets in the cells and improves myelination in mice.

And in September in *Nature*, von Maydell extended the lab's studies of lipid-caused Alzheimer's pathology and symptoms to the ABCA7 gene, which encodes a protein that transports lipids across cell membranes. Looking at gene expression changes in the brains of a dozen people with rare ABCA7 mutations, the team saw ominous effects on lipid metabolism, DNA damage, and mitochondrial function in neurons.



Postmortem brain tissues stained for myelin for a 2022 study show that APOE3 carriers (top row) had much better myelination than APOE4 carriers (bottom)

Similar changes were also evident in neurons they cultured with ABCA7 mutations in the lab, which also exhibited hyperactivity and excessive amyloid secretion. A key aspect of the pathology turned out to be metabolism of phosphatidylcholine, which helps make membranes, including for mitochondria, potentially explaining their problems. As with the astrocytes, supplements of choline helped correct the process in neurons. Amyloid and hyperactivity in cell cultures went down.

Going further with fats

Tsai notes that after years out of the clinical spotlight, lipids are now a focus at many pharmaceutical and startup companies.

And the Tsai lab is working on many new angles, too. In collaboration with MD Anderson Hospital in Houston and the University of Texas, Tsai has been testing choline in clinical studies with volunteers who have APOE4. The first round established useful biomarkers to set the table for a larger study that, if funded, will test for benefits.

Her lab is also using CRISPR to screen for genes or pathways that can be perturbed to help reverse the effects of APOE4 in different cell types. Von Maydell is leading an effort to employ artificial intelligence to better cluster Alzheimer's patients in hopes of identifying subgroups that would be especially responsive to treatments. And former postdoc Rebecca Pinals, who just started her own lab at Stanford, is looking at molecular means of intervening in how lipids are trafficked in Alzheimer's brains.

Given how closely many of us watch our fat intake (and accumulation), we might wonder whether lifestyle and diet changes could help, too. Tsai says indeed exercise and a healthy diet are considered protective but the exact mechanisms aren't yet clear. Another MIT project could help. Researchers in the Mechanical Engineering Department and in Tsai's lab have teamed up to develop an AI tool that will combine a huge international study of preventative lifestyle factors with gene expression and other biological "-omics" data for cross-cutting analyses. In October their plan became one of 10 semifinalists out of 200 entries in a $1 million contest funded by Bill Gates.

Around our waists, we often see fat as something to fight. In our heads, however, the game is a little more complex: Fats are everywhere, but in each cell type they need to be in the right balance and in the right forms and places. Figuring out how to ensure that could produce major advances against Alzheimer's disease.

Upcoming EVENTS

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

2026 COLLOQUIUM ON THE BRAIN & COGNITION SERIES

THE PICOWER INSTITUTE FOR LEARNING AND MEMORY

March 19, 2026
Christopher Harvey, PhD
Harvard University
Hosted by Linlin Fan

April 30, 2026
Priya Rajasethupathy, PhD
The Rockefeller University
Hosted by Li-Huei Tsai

May 7, 2026
Larry Zipursky, PhD
UCLA
Hosted by Brady Weissbourd

All seminars begin at 4:00pm in Singleton Auditorium (46-3002) and on Zoom, followed be a reception in the Atrium.

Save the Date:
May 19, 2026

The Neuroscience of Democracy

THE PICOWER INSTITUTE FOR LEARNING AND MEMORY

Freedom Together Foundation

A joint symposium of
The Picower Institute
for Learning and Memory
and The Freedom Together Foundation

MIT Building 46, Singleton Auditorium

THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY

Printed on
30% recycled paper

Non Profit Org.
US Postage
PAID
Permit No. 1325
Boston, MA

Massachusetts Institute of Technology
77 Massachusetts Avenue Building 46 Room 1303
Cambridge, MA 02139-4307

picower.mit.edu

Neuroscience News Winter 2025

OUR VISION

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, behavior, and consciousness. Institute neuroscientists explore the brain and nervous system 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.

SUPPORT THE PICOWER INSTITUTE

For more information on our research or how to make a gift to The Picower Institute for Learning and Memory, please contact:
Asha Bhakar, PhD, abhakar@mit.edu, Tel: 617-258-0759.

HOW TO SUBSCRIBE

Subscriptions to Neuroscience News are available at no charge in print or PDF form. To subscribe, send your mailing or email address to: Darnell Reese, drreese@mit.edu, Tel: 617-452-2485.

EDITORIAL CONTRIBUTORS

David Orenstein, Anne Trafton, and Bendta Schroeder

CONTACT THE PICOWER INSTITUTE

The Picower Institute for Learning and Memory
Massachusetts Institute of Technology,
77 Massachusetts Avenue, Building 46, Room 1303,
Cambridge, MA 02139-4307, Tel: 617-324-0305 picower.mit.edu

TOP ROW: **Mark F. Bear**, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences; **Emery Brown**, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience, Department of Brain and Cognitive Sciences, Institute of Medical Engineering and Science core faculty; **Gloria Choi**, Associate Professor, Department of Brain and Cognitive Sciences; **Kwanghun Chung**, Eugene McDermott Professor, Departments of Chemical Engineering and Brain and Cognitive Sciences, Institute of Medical Engineering and Science core faculty; **Linlin Fan**, Samuel Goldblith Assistant Professor, Department of Brain and Cognitive Sciences; **Steven Flavell**, HHMI Investigator, Associate Professor, Department of Brain and Cognitive Sciences; **Myriam Heiman**, John and Dorothy Wilson Professor of Neuroscience, Department of Brain and Cognitive Sciences; **Troy Littleton**, Menicon Professor of Biology and Neuroscience, Departments of Biology and Brain and Cognitive Sciences.

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, Departments of Brain and Cognitive Sciences and Biology; **Sara Prescott,** Assistant Professor of Biology; **Mriganka Sur**, Paul E. Newton Professor of Neuroscience, Director of The Simons Center for the Social Brain, Department of Brain and Cognitive Sciences; **Susumu Tonegawa**, Picower Professor of Biology and Neuroscience, Departments of Brain and Cognitive Sciences and Biology, HHMI Investigator, 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; **Brady Weissbourd,** Assistant Professor of Biology; **Matthew Wilson**, Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology, Associate Director, The Picower Institute for Learning and Memory.