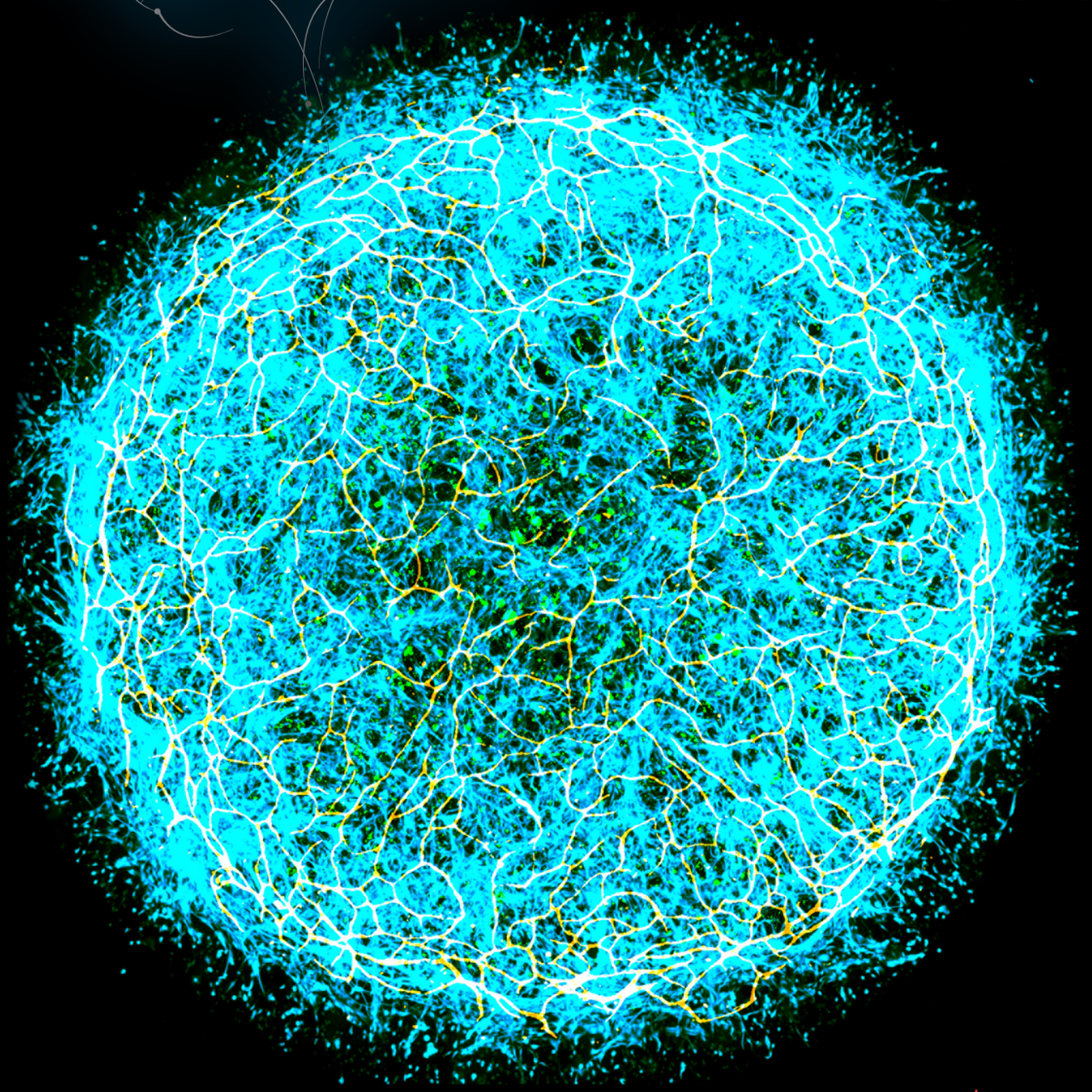
Aging Brain Initiative

NEWS 2025



/ Inside /

From the Director

Dear Friends,

We launched The Aging Brain Initiative 10 years ago as a collaborative, cross-campus effort at MIT, with a commitment to whole systems research on brain aging and dementia. Our goal has been to reduce the impact of cognitive decline, alleviate patient suffering, and address global dementia-related medical costs. The ABI is unique as it integrates research from the fields of neuroscience, genetics, biology, computer science, urban planning, chemistry, engineering, medicine and finance.

This year, we were excited to fund five new projects across MIT, through our seed funding program made possible by generous gifts to the Aging Brain Initiative Fund. You can read more about their projects on page 14. And you can learn about many individual advances and insights, from technological inventions to potential therapies and clinical trials as you read through the newsletter.

These efforts are made possible not only by the ingenuity and hard work of the MIT research community, but also by your enduring support. Thank you from all of us and we hope you enjoy reading this year's newsletter.

Li-Huei Tsai,
Director, The Aging Brain Initiative

On the cover: ***miBrain is a 'human multicellular integrated brain' model built with an engineered 3D hydrogel that can support all six major brain cell types. A modular system, miBrain is ideal for testing therapeutic efficacy and drug delivery. See story on page 7.***

ABI Symposium:
New treatment ideas lie along neuro-immune axis

Understanding how interactions between the central nervous system 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.

"The past decade has brought rapid progress in our understanding of how adaptive and innate immune systems impact the pathogenesis of neurodegenerative disorders," said Picower Professor Li-Huei Tsai, director of The Picower Institute and the Aging Brain Initiative, in her introduction to the event, which packed MIT's Singleton Auditorium. "[Our speakers'] work converges on the promise of immunology-informed therapies to slow or prevent neurodegeneration and age-related cognitive decline."

Keynote speaker Michal Schwartz of the Weizmann Institute described her decades of pioneering work to understand the neuro-immune "ecosystem." Her lab 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, Tsai described recent work from her lab and that of computer science Professor and fellow ABI member Manolis Kellis 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.

"Genetic risk, epigenomic instability and microglia exhaustion really play a central role in Alzheimer's disease," Tsai said.

The neuro-immune "axis" connects not only the nervous and immune systems, but also extends between the whole body and the brain with numerous implications for aging. Several speakers, including MIT Biology Assistant Professor Sara Prescott, focused on the key conduit: the vagus nerve, which runs from the brain to the body's major organs. And several other speakers discussed opportunities for understanding neuro-immune interactions in aging and disease at the "borders" where the brain's and body's immune system meet.

Sara Prescott begins her talk on the airway-brain axis at the 2025 ABI Symposium.

Alzheimer's erodes brain cells' control of gene expression, undermining cognition

A sweeping study in *Cell* paints a high-resolution picture of Alzheimer's disease as a desperate struggle to maintain healthy gene expression and gene regulation, where the consequences of failure or success are nothing less than the loss or preservation of cell function and cognition.

The study presents a first-of-its-kind, multimodal atlas of combined gene expression and gene regulation spanning 3.5 million cells from six brain regions, obtained by profiling 384 post-mortem brain samples across 111 donors. The researchers profiled both the "transcriptome," showing which genes are expressed into RNA, and the "epigenome," the set of chromosomal modifications that establish which DNA regions are accessible and thus utilized between different cell types.

The resulting atlas shows that the progression of Alzheimer's is characterized by two major epigenomic trends. The first is that vulnerable cells in key brain regions suffer a breakdown of the rigorous nuclear "compartments" they normally maintain to ensure that some parts of the genome are open for expression but others remain locked away. The second major finding is that susceptible cells experience a loss of "epigenomic information," meaning they lose their grip on the unique pattern of gene regulation and expression that gives them their specific identity and enables their healthy function.

Accompanying the evidence of compromised compartmentalization and the erosion of epigenomic information are many specific findings pinpointing molecular circuitry that breaks down by cell type, by region, and gene network. The Aging Brain Initiative scientists found, for instance, that when epigenomic conditions deteriorate, that opens the door to expression of many genes associated with disease, whereas if cells manage to keep their epigenomic house in order, they can keep disease-associated genes in check. Moreover, the researchers clearly saw that when the epigenomic breakdowns occur people lost cognitive ability, but where epigenomic stability remained, so did cognition.

The lab of **Manolis Kellis**, a professor in the Computer Science and Artificial Intelligence Lab and head of MIT's Computational Biology Group, led the study. Picower Professor **Li-Huei Tsai** is a co-senior author.

Systems biology uncovers potential targets for Alzheimer's

MIT researchers led by Professor **Ernest Fraenkel**, in collaboration with Mel Feany's lab at Harvard Medical School, have identified new potential targets for treating Alzheimer's disease. Their unique approach started with a genome-scale 'forward genetics' screen to hunt down genes that can be linked to neurodegeneration in fruit flies. They then integrated their results with multi-omics data from patients with Alzheimer's. Their work linked about 200 fruit fly genes to neurodegeneration, many of which also decline with age in humans.

Their discoveries highlight the need for multi-target treatments that target factors beyond amyloid. Fraenkel noted "even if the amyloid hypothesis is correct — and there are some people who don't think it is — you need to know what those other factors are. And then if you can hit all the causes of the disease, you have a better chance of blocking and maybe even reversing some losses."

The team hopes to accelerate drug development using improved experimental models and computational tools, potentially leading to significant breakthroughs. The study, published in *Nature Communications*, was led by Matthew Leventhal (PhD '25).

A sensory approach to boost cognition in Down syndrome

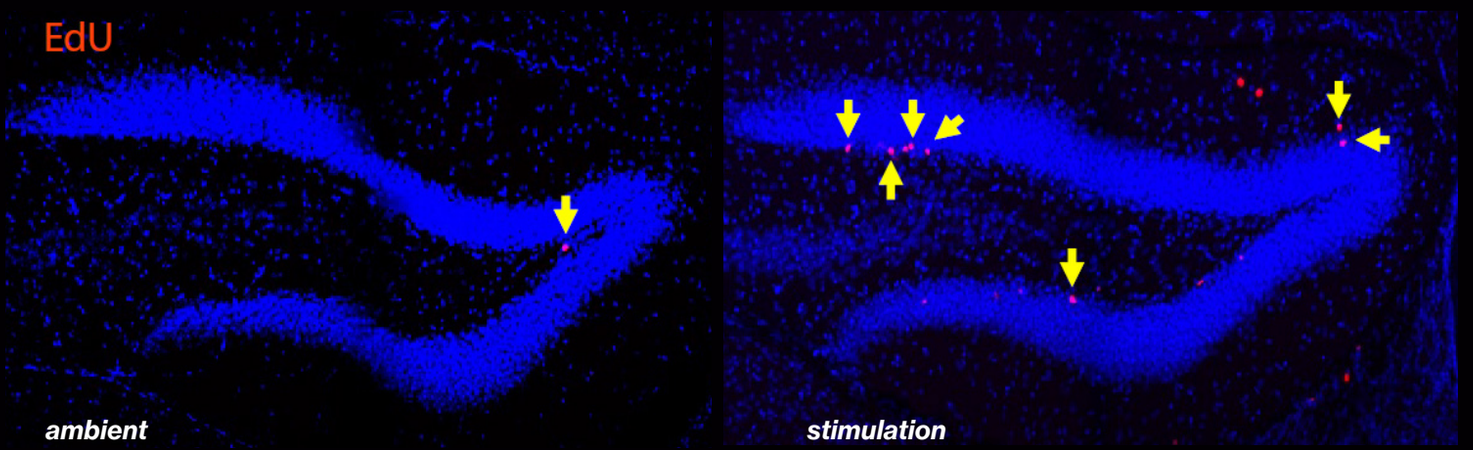
Recent research from the Alana Down Syndrome Center of MIT, led by **Li-Huei Tsai**, has found that 40Hz sensory stimulation—light and sound delivered at the brain's gamma frequency—can significantly improve cognition, brain connectivity, and neurogenesis in a mouse model of Down syndrome. This technique, known as GENUS (gamma entrainment using sensory stimulation), has previously shown promise in models of Alzheimer's disease and other neurological conditions.

The study, led by postdoc Reza Islam and Brennan Jackson (PhD '23) and published in *PLOS ONE*, used the Ts65Dn mouse model, which mimics key features of Down syndrome. Mice received one hour of daily 40Hz stimulation for three weeks. Treated mice performed better on short-term memory tasks involving spatial navigation and novelty recognition. These tasks rely on the hippocampus, where the researchers found increased neural activity in stimulated mice.

Using single-cell RNA sequencing, the team examined gene expression in nearly 16,000 cells and found changes linked to improved synaptic connectivity. In particular, the dentate gyrus region of the hippocampus showed a significant increase in synapses. The study also identified higher expression of the gene **TCF4**, a key regulator of neurogenesis, in stimulated mice. Correspondingly, these mice showed increased growth of new neurons.

Further analysis showed that GENUS-treated mice retained more neurons expressing **Reelin**, a protein tied to cognitive resilience in Alzheimer's disease—a relevant finding, as the **lifetime risk of developing Alzheimer's disease is over 90% for people with Down syndrome**.

While promising, lead author Li-Huei Tsai cautioned that more research is needed, especially in humans. The current mouse model does not fully replicate human Down syndrome, and the study focused only on male mice and short-term memory. Early human trials have been completed at MIT to investigate GENUS's safety and potential for helping adults with Down syndrome.



40 Hz stimulation boosts neurogenesis (red) in cells of the hippocampus (blue).

Evidence expanding that 40Hz stimulation promotes brain health

A decade after scientists in The Picower Institute for Learning and Memory at MIT first began testing whether sensory stimulation of the brain's 40Hz "gamma" frequency rhythms could treat Alzheimer's disease in mice, a growing evidence base supporting the idea that it can improve brain health—in humans as well as animals—has emerged from the work of labs all over the world. A review article in *PLOS Biology* described numerous independent studies and presented some of the fundamental and clinical questions at the forefront of the non-invasive gamma stimulation now.

"As we've made all our observations, many other people in the field have published results that are very consistent," said **Li-Huei Tsai**, Picower Professor at MIT, director of MIT's Aging Brain Initiative. "People have used many different ways to induce gamma including sensory stimulation, transcranial alternating current stimulation or transcranial magnetic stimulation, but the key is delivering stimulation at 40 Hz. They all see beneficial effects."

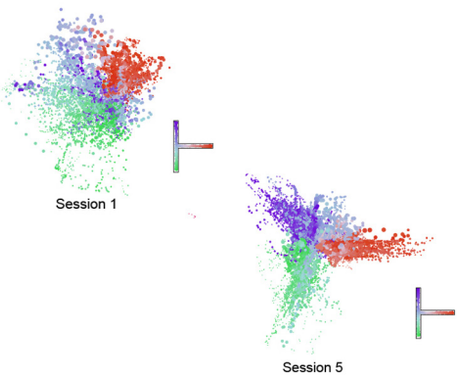
How the brain, with sleep, learns to map areas

A new study in mice provides new evidence for how the brain forms cohesive cognitive maps of whole spaces and highlights the critical importance of sleep for the process.

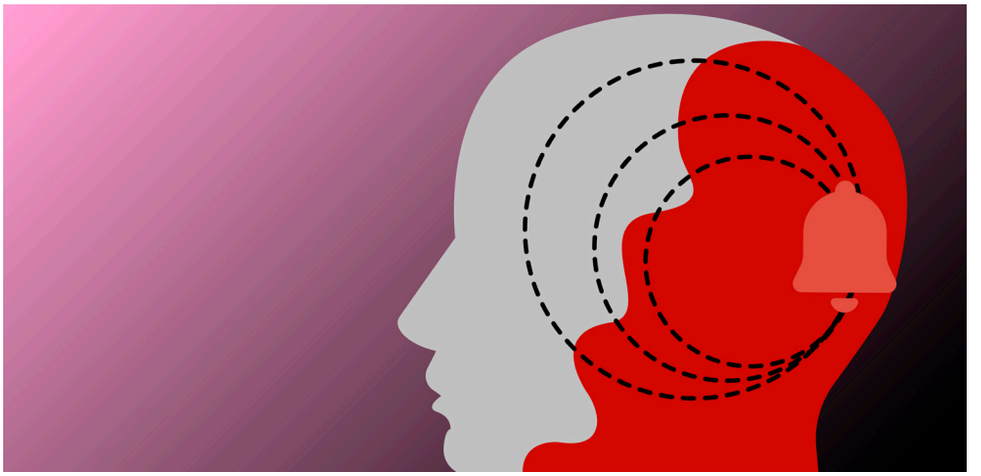
The research explains how we create a mental model of how individual locations all relate in a continuous overall geography. The new study *Cell Reports* found that the capability may depend upon subtle but meaningful changes over days in the activity of cells that are only weakly attuned to individual locations, but that increase the robustness and refinement of the hippocampus's encoding of the whole space. With sleep, these "weakly spatial" cells increasingly enrich neural network activity in the hippocampus to link together these places into a cognitive map.

"On day 1, the brain doesn't represent the space very well," said lead author Wei Guo, a research scientist in the lab of Sherman Fairchild Professor **Matthew Wilson**. "Neurons represent individual locations, but together they don't form a map. But on day 5 they form a map. If you want a map, you need all these neurons to work together in a coordinated ensemble."

Importantly, future studies will examine the effect of age on this learning mechanism - as both sleep and some forms of memory decline with aging.



Neural representations of a cognitive map of a sideways T-shaped maze evolved over five sessions. Each dot is a point in time and each color corresponds to a location in the actual maze (see smaller T's). Over time the cognitive map better resembles the actual maze geometry.



Anesthesia study reveals insights into conscious cognition

A new study examines how sensory processing works during consciousness and also breaks down under general anesthesia. The results add evidence for the idea that conscious thought requires synchronized communication—mediated by brain rhythms in specific frequency bands—between basic sensory and higher-order cognitive regions of the brain.

The new results in *PNAS*, show that when animals were under propofol-induced general anesthesia, a sensory region retained the capacity to detect simple surprises but communication with a higher cognitive region toward the front of the brain was lost, making that region unable to engage in its normal "top-down" regulation of the activity of the sensory region and keeping it oblivious to what the sensory region was reporting.

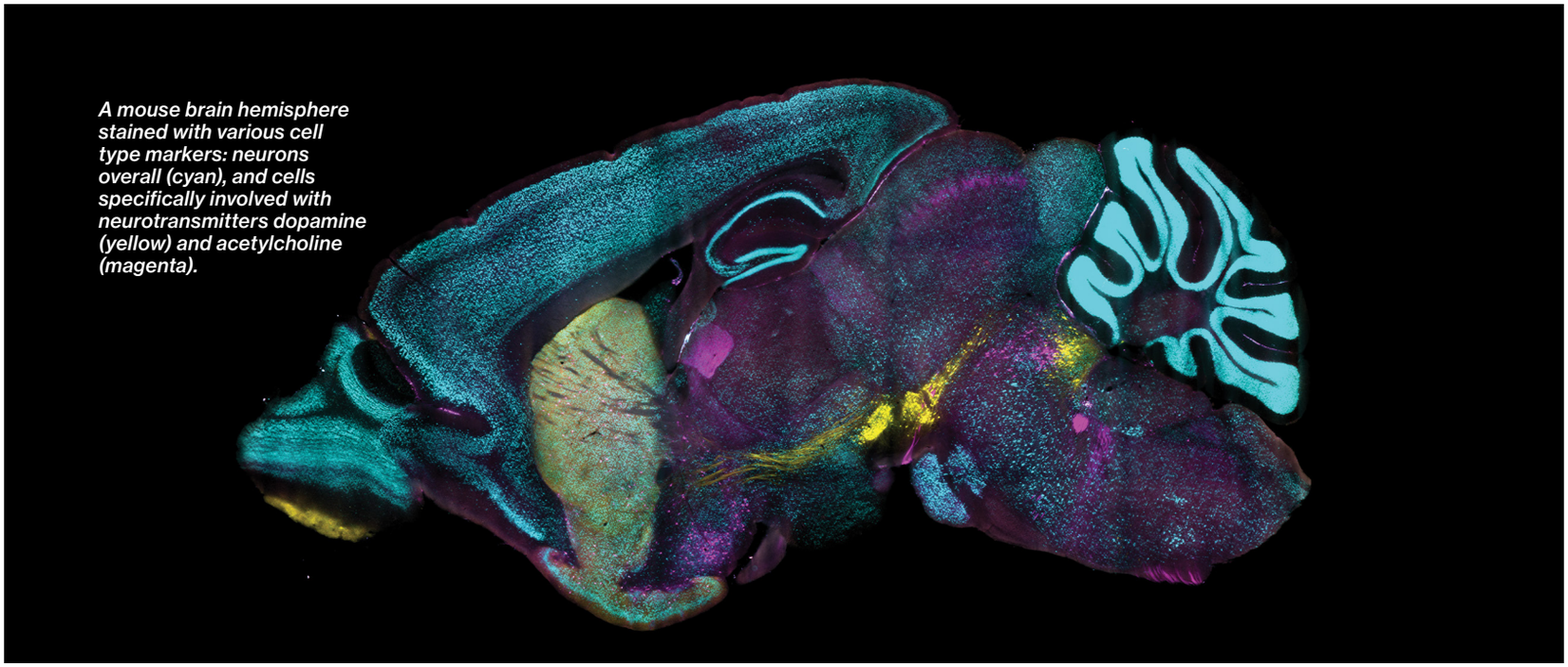
"Propofol general anesthesia deactivates the top-down processes that underlie cognition," said co-senior author and Picower Professor **Earl K. Miller**. "It essentially disconnects communication between the front and back halves of the brain." The effects of propofol change with aging, so future work may examine the effects of age on this top-down deactivation.

Anesthetics induce unconsciousness by shifting brainwave phase

Ketamine and dexmedetomidine are different chemicals, but they can each anesthetize a patient. By demonstrating how these distinct drugs achieve the same result, a new MIT study identifies a potential signature of unconsciousness that is readily measurable to improve anesthesiology care.

What the two drugs have in common, the researchers discovered, is the way they push around brain waves. When the electrical rhythms are in phase, local groups of neurons in the brain's cortex can share information to produce conscious cognitive functions such as attention, perception and reasoning, said Picower Professor **Earl K. Miller**, senior author of the new study in *Cell Reports*, along with colleague and Taplin Professor **Emery N. Brown**. When brain waves fall out of phase, local communications, and therefore functions, fall apart, producing unconsciousness.

The finding, not only adds to scientists' understanding of the dividing line between consciousness and unconsciousness, Miller said, but also could provide a common new measure for anesthesiologists who use a variety of different anesthetics to maintain patients on the proper side of that line during surgery.



A mouse brain hemisphere stained with various cell type markers: neurons overall (cyan), and cells specifically involved with neurotransmitters dopamine (yellow) and acetylcholine (magenta).

MIT enables protein labeling of tens of millions of cells in whole organ samples

A new technology developed at MIT and published in *Nature Biotechnology* enables scientists to label proteins across millions of individual cells in dense, fully intact 3D tissues with unprecedented speed, uniformity, and versatility. Using the technology, the team, led by Eugene McDermott Professor in the Brain Sciences and Human Behavior **Kwanghun Chung**, was able to richly label large tissue samples in a single day.

Profiling the proteins that cells are making is a staple of studies in biology, neuroscience and related fields because the proteins a cell is expressing at a given moment can reflect the functions the cell is trying to perform or its response to its circumstances, such as disease or treatment. But as much as microscopy and labeling technologies have advanced, scientists have still lacked a reliable and practical way of tracking protein expression at the level of millions of densely packed individual cells in whole, 3D tissues such as an entire mouse brain or a full region of a human brain.

The fundamental reason why large, 3D tissue samples are hard to label uniformly is that antibodies seep into tissue very slowly, but are quick to bind to their target proteins. The effect of this speed mismatch is that simply soaking a brain in a bath of antibodies will mean that proteins are intensely well labeled on the outer edge of the tissue, but virtually none of the antibodies will find cells and proteins deeper inside. MIT's new CuRVE and eFLASH technologies solve this by accelerating antibody dispersion with continuously modifiable binding speed. In all, the team reported using more than 60 different antibodies to label proteins in cells across whole brains of mice and rats; whole mouse embryos; other whole mouse organs including lung and heart; and blocks of brain tissue from larger animals including humans.

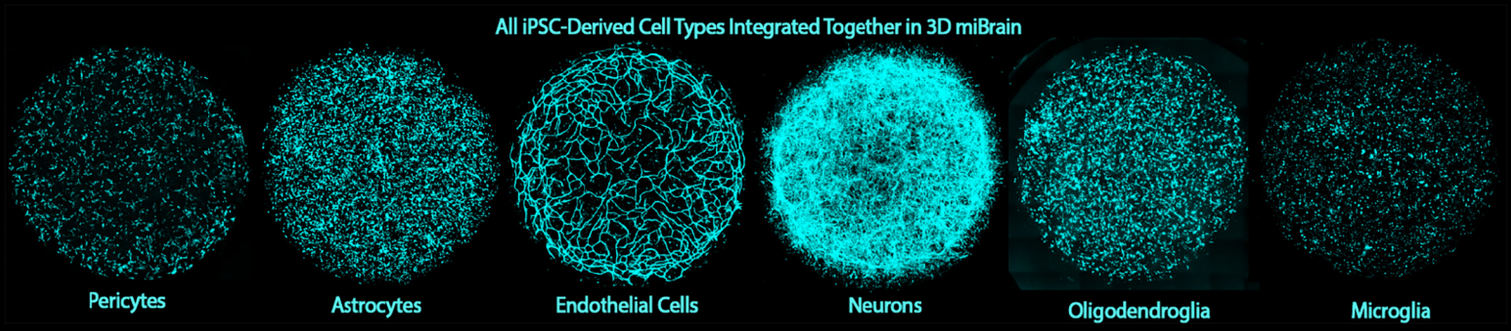
Dopamine signals when a fear can be forgotten

Dangers come but dangers also go and when they do, the brain has an "all-clear" signal that teaches it to extinguish its fear. A new study in mice by MIT neuroscientists shows that the signal is the release of dopamine along a specific interregional brain circuit. The research therefore pinpoints a potentially critical mechanism of mental health, restoring calm when it works, but prolonging anxiety or even post-traumatic stress disorder- a condition linked to an increased risk of Alzheimer's disease and dementia - when it doesn't.

In 2020, the lab of Picower Professor and senior author **Susumu Tonegawa** showed that learning to be afraid, and then learning when that's no longer necessary, result from a competition between populations of cells in the brain's amygdala region.

In the new study, the lab sought to determine what prompts these amygdala neurons to encode these memories. The rigorous set of experiments the team reports in the *Proceedings of the National Academy of Sciences* show that it is dopamine sent to the different amygdala populations from distinct groups of neurons in the ventral tegmental area (VTA).

"Our study uncovers a precise mechanism by which dopamine helps the brain unlearn fear," said co-lead author Xiangyu Zhang. "We found that dopamine activates specific amygdala neurons tied to reward, which in turn drive fear extinction. We now see that unlearning fear isn't just about suppressing it—it's a positive learning process powered by the brain's reward machinery. This opens up new avenues for understanding and potentially treating fear-related disorders like PTSD."



Individual labeling patterns of all six miBrain cell types.

New human brain model to enable personalized medicine

MIT researchers have developed *Multicellular Integrated Brains* (miBrains)—the first 3D human brain tissue model to include all six major brain cell types: neurons, astrocytes, oligodendrocytes, microglia, endothelial cells, and pericytes. Grown from donors' induced pluripotent stem cells, miBrains replicate the brain's cellular architecture, signaling, and vasculature in a single culture. Each model is smaller than a dime yet captures the complexity of human brain tissue, making it a powerful platform for studying neurological diseases and accelerating drug discovery.

A team led by Alice Stanton and Adele Bubnys, under the direction of MIT professors **Li-Huei Tsai** and **Robert Langer** and Joel Blanchard of Icahn School of Medicine, reported the study in the *Proceedings of the National Academy of Sciences*. The researchers engineered a hydrogel "neuromatrix" that mimics the brain's extracellular matrix, enabling the six cell types to self-assemble into functional immuno-glial-neurovascular units. This innovation bridges the gap between simple cell cultures, which lack key cellular interactions, and animal models, which are costly, slow, and biologically distinct from humans.

In their first application, the team used miBrains to study **APOE4**, the strongest genetic risk factor for 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, as expected. However, in APOE3 miBrains with APOE4 astrocytes, they found that APOE4 miBrains still exhibited amyloid and tau accumulation. Removing microglia or disrupting their signaling sharply reduced tau phosphorylation, revealing that immune cross-talk between astrocytes and microglia drives disease pathology.

Because miBrains are modular, each cell type can be genetically edited to represent specific patient genomes or disease variants, enabling personalized disease modeling. Stanton emphasized that miBrains' "precise control over cellular inputs, genetic backgrounds, and sensors" makes them ideal for testing therapeutic efficacy and drug delivery.

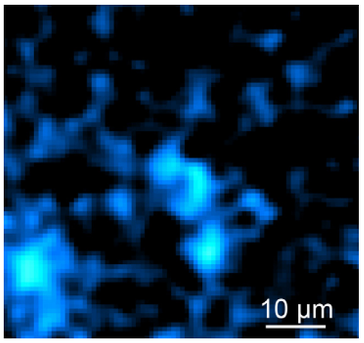
Two new horizons for expansion microscopy

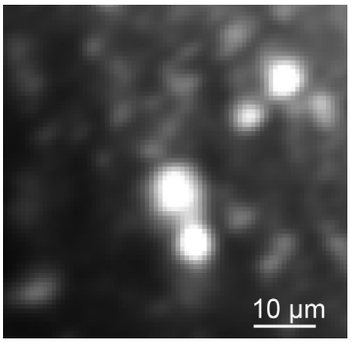
With two major advances published in *Nature Communications* this year, research teams in core ABI member **Ed Boyden's** lab are advancing **expansion microscopy (ExM)**, a technique they first introduced in 2015 that uses a water-absorbing hydrogel to physically enlarge tissue samples so crowded molecular structures become resolvable under a standard light microscope. ExM makes super-resolution imaging broadly accessible, and the team continues to refine its capabilities.

One breakthrough, **ultrastructural membrane expansion microscopy (umExM)**, enables visualization of thin lipid membranes that form cellular boundaries and organelles—structures previously hard to label in intact tissue. Developed by former graduate student Tay Shin (Phd '23), the method required engineering new molecular probes that link to lipids, the hydrogel, and fluorescent markers. This innovation lets researchers trace delicate neuronal features like dendrites and axons with clarity comparable to electron microscopy, but at far lower cost and complexity.

A second advance, **multiplexed expansion revealing (multiExR)**, allows simultaneous mapping of more than 20 proteins in the same tissue sample. By sequentially labeling proteins with fluorescent antibodies, imaging, and stripping the labels for reuse, researchers can build composite maps showing protein spatial relationships. Postdoc Jinyoung Kang and graduate student Margaret Schroeder optimized alignment strategies using vascular and structural features as landmarks, combined with custom software.

The team applied multiExR to Alzheimer's disease brain tissue, examining 23 different proteins in amyloid plaques and unexpectedly finding certain neurotransmitter receptors (AMPARs) within them. These tools promise to reveal previously hidden biological details, generating new hypotheses about cellular architecture, protein interactions, and disease mechanisms.





Imaging tech promises deepest look yet into living brain tissue at single-cell resolution

In a new study, an MIT team demonstrates a new microscope that uses sound to peer exceptionally deep into living brain tissues to detect the molecular activity of individual cells.

"The major advance here is to enable us to image deeper at single-cell resolution," said neuroscientist and Newton Professor **Mriganka Sur**, a corresponding author along with mechanical engineering Professor **Peter So** and principal research scientist Brian Anthony.

In the journal *Light: Science and Applications*, the team demonstrates that they could detect NAD(P)H, a molecule at the core of protection from age-induced oxidative damage, all the way through samples such as a 1.1 mm "cerebral organoid," a 3D-mini brain-like tissue generated from human stem cells, and a 0.7 mm thick slice of mouse brain tissue. Of note, the decline in this molecule is a potential biomarker of Alzheimer's disease.

A depth of 1.1 mm is more than five times deeper than what other microscope technologies can achieve for NAD(P)H within dense brain tissue. The scope excites NAD(P)H with "three-photon" long-wavelength light that can penetrate deeply with less scattering by brain tissue ("like fog lamps," Sur said). Meanwhile, the excitation causes thermal expansion within the cell, which produces sound waves that travel relatively easily through tissue compared to the fluorescence emission. A sensitive ultrasound microphone in the microscope detects those waves and, with enough sound data, software turns them into high-resolution images (much like a sonogram does). Notably, the approach doesn't require adding any external labels to resolve target molecules, either via added chemicals or genetically engineered fluorescence.

Above: In this edited version of a figure from the research, NAD(P)H molecules within cells in a cerebral organoid are detected photoacoustically (in blue on left) and optically (black and white on right). Image depth 0.2 mm.

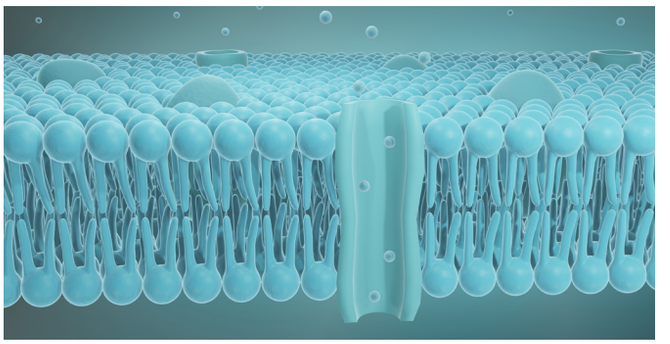
Unraveling ABCA dysfunction in Alzheimer's

A new MIT study has shed light on how rare variants of **ABCA7, a gene that encodes a lipid transporter,** contribute to Alzheimer's disease by disrupting lipid metabolism and cell membrane function in neurons. Dysfunctional ABCA7, present in a small fraction of the population, approximately doubles Alzheimer's risk by impairing lipid transport across membranes, leading to neuronal hyperexcitability, DNA damage, and oxidative stress.

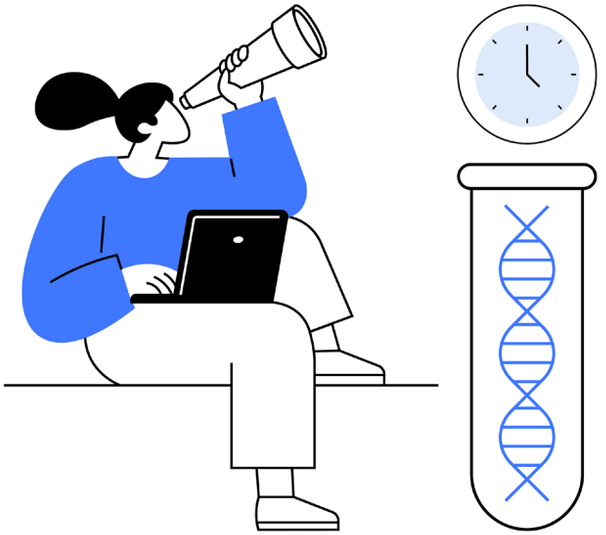
Using brain tissue samples from the Religious Orders Study and Rush Memory and Aging Project and neurons derived from induced pluripotent stem cells, researchers found that ABCA7 mutations altered expression of genes tied to lipid metabolism, oxidative phosphorylation, and DNA damage response. The affected neurons showed mitochondrial dysfunction, reduced ability to manage electrical charge buildup, and stiffened membranes due to changes in phosphatidylcholine metabolism.

Encouragingly, treatment with **CDP-choline**, a precursor to phosphatidylcholine, reversed many of these defects. Supplemented cells regained normal mitochondrial function, reduced oxidative stress, and lowered amyloid beta accumulation, a hallmark of Alzheimer's pathology. Organoids generated from ABCA7-mutant neurons also showed decreased hyperexcitability and amyloid beta levels after CDP-choline treatment. The findings build on earlier work showing that choline supplementation mitigates effects of the common Alzheimer's-linked **APOE4** gene. Since choline is found in foods like eggs, meat, fish, beans, and nuts, the study suggests that dietary or supplemental choline could help restore lipid homeostasis and reduce Alzheimer's risk.

Notably, even a more common ABCA7 variant—found in about 18 percent of people—showed similar lipid metabolism disruptions, indicating ABCA7 dysfunction may influence Alzheimer's risk in a broader population. This work, led by **Li-Huei Tsai** and graduate student Djuna von Maydell, was published in *Nature*.



ABCA7 is a transmembrane protein that transports lipids across cell membranes.



B vitamins, epigenetic clocks and brain aging

A recent *Aging Cell* study from Elysium Health, co-founded by ABI core member **Leonard Guarente**, has been focusing on a blood molecule called homocysteine. High levels of total homocysteine (tHcy) have long been linked to cognitive decline, brain shrinkage, and Alzheimer's disease. This study, part of the VITACOG trial, explored how tHcy relates to "epigenetic age" – a biological measure of how fast a person is aging, based on chemical tags (methylation) on their DNA. Researchers examined older adults with mild cognitive impairment and used several "epigenetic clocks" to estimate their biological aging rate. They found that people with higher tHcy were aging faster at the molecular level.

Importantly, participants who took daily B-vitamin supplements (vitamin B6, folic acid, and vitamin B12) – known to lower tHcy – showed a slowing of both brain shrinkage and epigenetic aging. A new measure called the "Index" clock revealed that this treatment effectively normalized the accelerated aging seen in those with high tHcy.

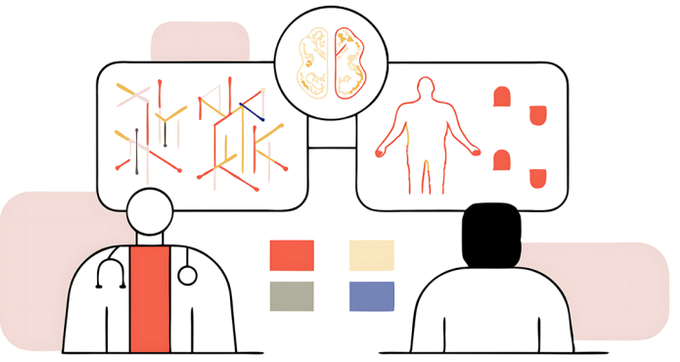
Because B-vitamins are inexpensive and safe, these results suggest a simple way to potentially protect brain health and slow biological aging in the many older adults worldwide with elevated tHcy levels. The findings also highlight how DNA methylation clocks can help track how lifestyle and nutritional factors influence the pace of aging, offering a promising new tool for understanding and possibly mitigating cognitive decline and age-related disease.

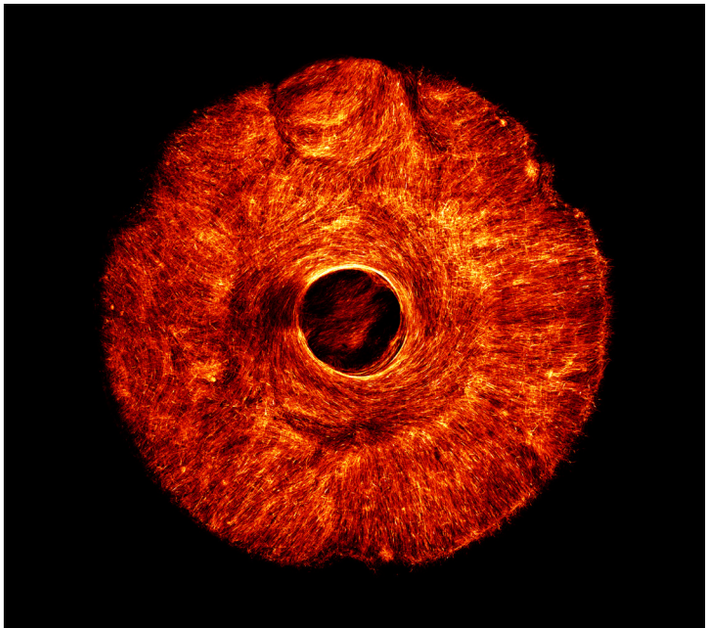
Mapping metabolites to solve disease

Biology's complexity extends far beyond genes to the proteins and metabolites that build and fuel cells. MIT spinout **ReviveMed**, founded by Leila Pirhaji (PhD '16) and Professor **Ernest Fraenkel**, has developed a platform to measure metabolites—molecules such as lipids, cholesterol, and sugars—at scale. By tapping into this underutilized data, the company aims to explain why patients respond differently to treatments and to reveal hidden drivers for diseases like cancer, Alzheimer's, and heart disease.

Historically, researchers could only measure a small fraction of metabolites with accuracy. Pirhaji confronted this gap during her PhD at MIT when faced with metabolomic datasets too ambiguous to interpret. She responded by building a massive knowledge graph of protein–metabolite interactions and devising methods to map metabolic pathways, publishing her findings in *Nature Methods* in 2016. Inspired by the technology's potential, she embraced MIT's entrepreneurial ecosystem and co-founded ReviveMed.

Since its founding, the company has partnered with major players in the pharmaceutical industry, including Bristol Myers Squibb, to predict patient responses to therapies and identify metabolic mechanisms of disease. Its platform accelerates drug development by matching the right patients to the right treatments, thereby reducing clinical trial costs and timelines. ReviveMed is also pioneering the use of generative AI in metabolomics. In 2025, it built 'digital twins' of patients from 20,000 blood samples to model disease and treatment effects. These models are being shared with academic researchers, democratizing metabolomic insights and pushing toward the creation of metabolic foundation models. Ultimately, ReviveMed's technology could transform precision medicine by systematically integrating metabolites into the study of health and disease.





Engineered muscle to help researchers understand ALS

An MIT team led by "**la Caixa" Foundation ABI fellow Tamara Rossy**, Laura Schwendeman and Assistant Professor **Ritu Raman** in the Department of Mechanical Engineering have developed **STAMP** (Simple Templating of Actuators via Micro-Topographical Patterning), a low-cost, one-step method to guide how muscle cells grow and align on soft materials. Using reusable 3D-printed stamps, STAMP can precisely pattern the microtopography of hydrogels, eliminating the need for expensive equipment or complex fabrication steps. The team showed that STAMP can align both mouse and human muscle fibers without harming their growth or function. To demonstrate its potential, they built a soft robotic "iris" that when combined with the power of optogenetics, opens and closes in response to light. Their accomplishment showcases how engineered muscle tissues can drive complex, lifelike movements.

Rossy is now using the patterned muscle to advance an in vitro model of the neuromuscular interface in order to study the pathogenic mechanisms underlying amyotrophic lateral sclerosis (ALS). Once developed, her system will allow her to closely model exercise's impact and potential as a therapy for ALS and other neurodegenerative diseases.

The work was published in *Biomaterials Science*.

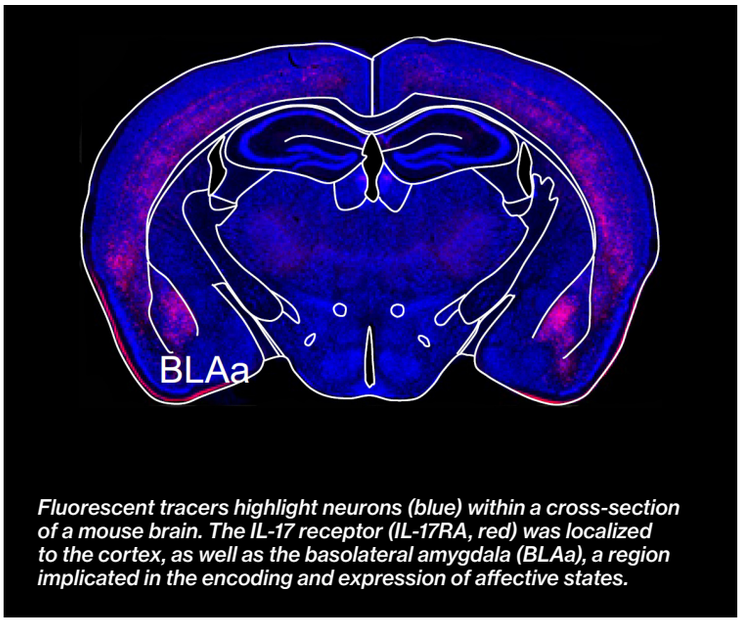
Above: Mouse muscle stem cells growing on a fibrin substrate stamped with an iris-like micro-grooved pattern.

Interconnections revealed between the immune system and behavior

Two new studies from MIT and Harvard Medical School have revealed how the immune molecule IL-17 influences brain function and behavior, highlighting deep connections between the immune and nervous systems. IL-17, a cytokine that helps regulate inflammation, acts on two brain regions with contrasting effects: in the amygdala, it provokes anxiety, while in the somatosensory cortex, it promotes sociability. Importantly, IL17 comes in six different forms, and there are five different receptors that it can bind to.

MIT neuroscientist **Gloria Choi** and Harvard immunologist Jun Huh, senior authors of the studies published in *Cell*, discovered that different IL-17 subtypes and receptor combinations drive these divergent behaviors. In earlier work, they found that IL-17 suppresses overactive neurons in a small cortical region (S1DZ) linked to autism-like behaviors in mice. The new research shows that one form on IL-17, IL-17E, binds to the IL-17RA and IL-17RB receptors in this region, dampening neuronal excitability and increasing social behavior—acting much like a neuromodulator rather than a traditional immune signal. On the other hand, two other forms of IL-17, IL-17A and IL-17C, bind to IL-17RA and IL-17RE receptors in the amygdala, boosting neuronal excitability and increasing anxiety. This reaction may serve an evolutionary purpose by encouraging sick individuals to isolate and prevent spreading infection.

Choi's lab also found that anti-inflammatory cytokine IL-10 counteracts IL-17-induced anxiety, suggesting a built-in balance mechanism. Together, these findings indicate that cytokines like IL-17 can fine-tune neural circuits to produce adaptive behavioral responses during illness. The research opens new avenues for treating neurological and psychiatric disorders—by targeting immune pathways to modulate brain activity, rather than acting directly on neurons.



Fluorescent tracers highlight neurons (blue) within a cross-section of a mouse brain. The IL-17 receptor (IL-17RA, red) was localized to the cortex, as well as the basolateral amygdala (BLAa), a region implicated in the encoding and expression of affective states.

A volunteer receives 40 Hz light and sound stimulation while being monitored with an EEG.

New study on the long-term use of 40 Hz therapy

A new study reports long-term outcomes for five volunteers who continued receiving daily 40Hz light and sound stimulation, known as GENUS (gamma entrainment using sensory stimuli), for about two years following MIT's early-stage Alzheimer's trial. Three female participants with late-onset Alzheimer's showed meaningful benefits compared to matched national database controls, including better cognitive scores, improved circadian rhythms, stronger brain-wave responses, and reduced Alzheimer's biomarkers. In two who provided blood samples, phosphorylated tau (pTau217)—a key FDA-approved plasma biomarker—declined by 47% and 19%. By contrast, the two male participants with early-onset Alzheimer's did not experience significant improvements and showed weaker brain responses to stimulation, suggesting GENUS may be less effective in this form of the disease but importantly, future work is warranted to test whether 40Hz can be used as a preventative therapy in those at risk for early-onset AD.

The study, published in the *Journal of the Alzheimer's Association*, represents the longest test to date of this safe, non-invasive therapy, which builds on years of animal research showing 40Hz stimulation can enhance gamma brain activity, protect neurons, and reduce Alzheimer's proteins. MIT's original 2020 trial with 15 patients demonstrated cognitive benefits after three months, though it was shortened by the pandemic.

Led by clinical fellow **Diane Chan** of The Picower Institute and Massachusetts General Hospital, with senior author **Li-Huei Tsai**, the research supports continued evaluation of GENUS in larger, randomized trials, which are now underway through Cognito Therapeutics. The findings suggest that multimodal 40Hz stimulation may slow decline and alter disease biology, particularly in late-onset Alzheimer's patients.

Participate in GENUS trials

Researchers at MIT and Mass General Hospital (MGH) are recruiting participants for two clinical trials that will test Gamma ENtrainment Using Sensory stimuli (GENUS), a non-invasive treatment with 40Hz light and sound stimulation, as a possible preventative or therapeutic strategy for Alzheimer's disease.

The first study is at MGH and is recruiting cognitively normal individuals who are 55-90 years old **who have an immediate family member** (biological parent or sibling) **with Alzheimer's disease**. The work is being conducted to see if GENUS can prevent progression to dementia in people who are currently cognitively healthy but are at risk for developing dementia. Over a 1-year period, eligible study participants will use the GENUS light and sound device at home daily for 1 hour. Study visits will include blood tests, scans of the brain to look for amyloid and tau proteins, MRI pictures of the brain, EEGs, cognitive assessments, and sleep assessments.

The second study is at MIT and is recruiting participants **who have been diagnosed with mild Alzheimer's disease.** The study will last 6 months with 3 required visits to the institution. Visits will include blood tests, fecal samples, EEGs, MRIs, memory and cognitive tests, and questionnaires to monitor progress. Participants will take home a GENUS device to use for 60 minutes daily as well as a watch to wear to track sleep patterns. Half of the participants will receive sham treatment. The purpose of this study is to determine whether gamma entrainment through non-invasive 40Hz sensory stimulation is possible in those with AD, and whether functional connectivity in their brain and molecular biomarkers of AD will change after 6 months of daily treatment.

Follow the **QR code** above for more details.

40 Hz clinical trial analyzes time delay in Alzheimer's progression

This June, Cognito Therapeutics, the Cambridge startup company that has licensed MIT's 40Hz sensory stimulation technology, reported a post-hoc analysis of their phase II clinical trial. OVERTURE was a 6-month randomized feasibility trial involving 76 participants with mild-to-moderate Alzheimer's disease (AD), which tested whether non-invasive sensory stimulation designed to evoke gamma oscillations could slow disease progression. Participants received either active daily light and sound stimulation or a sham treatment. Although the study did not reach statistical significance on its primary composite cognitive-functional measure (MADCOMS), the active group showed slower decline on several secondary outcomes: the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL), Mini-Mental State Examination (MMSE), and whole-brain volume.

This post hoc analysis further investigated those differences in terms of "time saved"—how long it would take for the treated group to reach the same level of decline as the control group. Using mixed-effects models, researchers estimated that over the six months of treatment, participants receiving active stimulation experienced an effective delay of 4.8 months in functional decline (ADCS-ADL), 4.6 months in cognitive decline (MMSE), and 4.1 months in brain atrophy. When data from the open-label extension (OLE) phase were included, the estimated time savings increased to 8.7, 10.0, and 7.5 months, respectively, across roughly 14–16 months of continued therapy.

These findings suggest that daily sensory-evoked gamma stimulation may meaningfully slow cognitive, functional, and structural brain deterioration in AD. Expressing benefits as "time saved" provides a patient-centered metric that makes treatment effects easier to interpret for patients, caregivers, and clinicians. Further research in larger, longer trials is warranted to confirm these preliminary results and to better understand the biological mechanisms linking gamma oscillations to neuroprotection in Alzheimer's disease. The HOPE trial (*see story on right*) has now completed enrollment in this larger effort.

Cognito was co-founded by MIT Professors and ABI founding members **Li-Huei Tsai** and **Ed Boyden**.

A pivotal study of sensory stimulation in Alzheimer's disease completes enrollment

This July, Cognito Therapeutics announced that they have completed enrollment in their pivotal HOPE study, evaluating the safety and efficacy of their non-invasive Spectris neuromodulation system for Alzheimer's disease. The trial enrolled 670 participants across 70 U.S. sites, making it the largest medical device study focused solely on Alzheimer's. HOPE is a randomized, double-blind, sham-controlled trial with a 12-month open-label extension planned. Spectris delivers synchronized gamma frequency light and sound stimulation designed to restore disrupted brain oscillations seen in Alzheimer's and slow disease progression. Building on positive results from the earlier OVERTURE study, Cognito aims to establish Spectris as a new therapeutic option for neurodegenerative diseases. CEO Christian Howell called the milestone a major step toward better treatments for people living with Alzheimer's.

"Hospice is saving Medicare a lot of money," says Jonathan Gruber, an MIT health care economist.

The international longevity hubs described in a new collection of essays edited by Luke Yoquinto (left) and Joe Coughlin represent successful, ongoing efforts to address the needs of older consumers.

The economics of care examined

The U.S. and much of the world face a looming crisis in elder care as populations age rapidly, with the share of people over 65 — and especially over 85 — rising sharply. In a new book *Long-Term Care around the World*, Ford Professor of Economics **Jonathan Gruber** and Stony Brook's Kathleen McGarry highlight how different countries address this challenge. In the U.S., about one-third of elder care is informal, provided by family and friends, despite high costs, stress and insufficiency. Nursing homes house just 1.2 million people. Private long-term care insurance has largely failed, covering few and offering limited benefits. Gruber argues the U.S. lacks mid-level "congregate housing" options, leaving many elders isolated and families overburdened. International comparisons show the U.S. spends moderately, but not strategically, on care. Gruber calls for greater investment in elder communities, framing it as a bipartisan, economically beneficial solution.

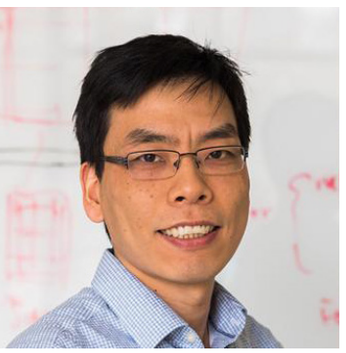
In 2025, Gruber also published a study focused on the economics of end-of-life care. The investigation highlighted hospice care's dual role in improving end-of-life experiences and reducing U.S. health care spending. Hospice, which prioritizes comfort over medical intervention, was found to save Medicare an estimated $29,000 per patient with Alzheimer's disease and related dementias (ADRD) in the five years post-diagnosis. The study, published in the *American Economic Review*, analyzed over 10 million patients from 1999–2019, comparing nonprofit, for-profit, and non-hospice care. It found that hospice neither extends life nor worsens outcomes, but instead operates as intended: reducing suffering while lowering costs. For-profit hospice providers have grown rapidly, now serving a large share of ADRD patients, though concerns about fraud and aggressive recruitment persist. Current Medicare reimbursement caps aim to limit abuse but may inadvertently harm patients by forcing premature hospice discharges. The researchers argue for more targeted fraud prevention tools. Overall, hospice emerges as a rare model that enhances quality of care while saving money.

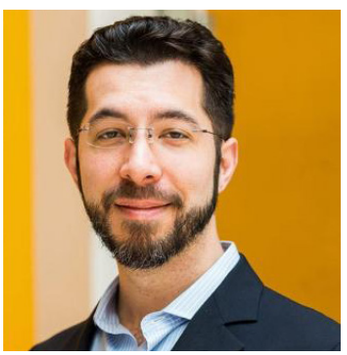
The making of Longevity Hubs

Boston has emerged as a leader in the "longevity economy," the rapidly expanding market for products and services serving older adults. In 2018, Inc. Magazine identified MIT's AgeLab, directed by Professor **Joseph Coughlin**, as a key driver of Boston's success, prompting AgeLab to collaborate with *The Boston Globe* on a yearlong series called *The Longevity Hub*. This project explored what would be required to make Boston the "Silicon Valley of aging." Building on that work, MIT Press recently published *Longevity Hubs: Regional Innovation for Global Aging*, which combines the Globe articles with new essays from an international set of contributors highlighting global efforts.

The book examines why innovation "clusters" form around aging economies and identifies tacit knowledge — awareness of the older market and strategies to serve it — as a critical factor. Beyond Boston, it highlights hubs in Louisville, Kentucky; Newcastle, U.K.; and São Paulo, Brazil, each fostering unique models of aging innovation. As global populations age, these hubs showcase both the challenges and vast opportunities of serving older consumers. The book was edited by Coughlin and Luke Yoquinto of MIT's AgeLab.





MIT faculty leading the new research projects. Top row left to right: Joe Coughlin, Giovanni Traverso, Pattie Maes. Bottom rows left to right: Bin Zhang, Laura Kiessling and Edward Boyden. Images from various sources including Justin Knight.

Five new projects supported by The Aging Brain Initiative Fund

Neurodegenerative diseases like Alzheimer's profoundly affect millions of families worldwide. To tackle the complex challenges these conditions present, MIT's Aging Brain Initiative (ABI) has awarded **$400,000 in seed grants to launch five cross-disciplinary projects.**

Several projects harness artificial intelligence (AI). Germeshausen Professor of Media Arts, **Pattie Maes**, is refining a wearable, voice-powered AI assistant that offers personalized reminders to older adults experiencing memory lapses. A four-week trial in senior living facilities will test how the device supports daily life and helps document memory issues in natural settings. Associate Professor **Bin Zhang** of Chemistry will apply AI to integrate diverse molecular datasets from postmortem Alzheimer's brains—gene expression, DNA accessibility, and 3D DNA structure—to uncover causal mechanisms of cellular dysfunction. Meanwhile, Mechanical Engineering Professor **Giovanni Traverso** and **Adrian Noriega de la Colina** will analyze blood proteins from a major 11-year Finnish study of seniors who underwent lifestyle interventions. Their AI-powered work aims to identify predictive biomarkers and clarify which health strategies most effectively protect cognition.

Beyond AI, other projects focus on protective and preventive factors. **MIT AgeLab Director Joe Coughlin** and his team will conduct a national survey to assess public awareness of lifestyle behaviors—such as education, diet, exercise, and social connection—that may reduce dementia risk. The results will inform education campaigns, professional guidance, and public policy. At the molecular level, Novartis Professor of Chemistry **Laura Kiessling** and Y. Eva Tan Professor of Neurotechnology **Ed Boyden** are investigating how sugar molecules known as heparan sulfate proteoglycans interact with proteins in the brain. By comparing healthy and diseased brains, they aim to reveal mechanisms of natural resistance to Alzheimer's and inspire new therapies.

Together, these five projects exemplify MIT's collaborative approach, leveraging cutting-edge science, engineering, and public engagement to address the urgent global challenge of Alzheimer's disease and the aging brain.

Gloria Choi

Arati Prabhakar awards Professor Emery Brown the National Medal of Science on Jan. 3. Credits: Photo: Ryan K. Morris / National Science and Technology Medals Foundation

Linlin Fan

Gloria Choi earns Samsung Ho-Am Prize

This year the Ho-Am Foundation selected **Gloria Choi**, Associate Professor in The Picower Institute, to receive the 2025 Samsung Ho-Am Prize for Medicine, one of the highest scientific honors in South Korea.

Choi's research focuses on neuroimmunology, the study of the bilateral communication between the immune and central nervous systems.

"[Choi] is a leading neuroscientist who has made groundbreaking contributions to our understanding of neurodevelopmental disorders," the foundation said in an April 2 announcement. "Through research using animal models, she uncovered a critical link between the immune system and brain health. Her findings reveal that, while excessive activation of the immune system during pregnancy can disrupt normal brain development, the immune system can also be harnessed to help alleviate autism symptoms. Dr. Choi's ongoing work to unravel the complex interactions between the nervous and immune systems holds great promise for the development of novel strategies to prevent and treat disorders such as autism, depression, and dementia."

Emery N. Brown earns National Medal of Science

On Jan. 3, 2025 neuroscientist, anesthesiologist and statistician **Emery N. Brown**, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience, won the National Medal of Science, the nation's highest recognition for scientists and engineers.

"This is an enormous pleasure to be recognized by the President with this high honor," said Brown, who shares this year's honor with three MIT colleagues and 23 colleagues around the country in total.

Brown's official citation, as read to an audience at the White House during a ceremony, was: "The National Medal of Science has been awarded to Emery Neal Brown for his revolutionary contributions to neuroscience and anesthesiology. Emery Brown's neuroscientific approach to understanding anesthesia's exact impact on the brain has been transformational for relieving patient suffering and has provided a new foundation for how we think about the very thing that makes us human, our consciousness."

Searle Scholar award funds study of serotonin in memory

There is a paradox in the brain's role as a memory making organ: It has to be flexible, or "plastic," enough to incorporate new information yet stable enough to keep the information it stores enduringly available. With a new Searle Scholar Award, MIT neuroscientist **Linlin Fan** will launch a study to determine how the neuromodulatory chemical serotonin may help the brain overcome the challenge.

'We are interested in studying brain-state-dependent plasticity rules, and serotonin can powerfully modulate brain states," said Fan an Assistant Professor in The Picower Institute.

Signs of serotonin's influence on memory encoding have been hard to measure in mice with enough precision to study and establish as a causal influence, especially during a live behavior like navigating and learning a new space. But Fan's lab specializes in advanced optical techniques that can simultaneously use light both to finely control and sensitively measure the subtleties of electrical and neuromodulatory chemical activity that govern neuronal plasticity.

Aging Brain Initiative

Massachusetts Institute of Technology

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picower.mit.edu/about/aging-brain-initiative

About the Aging Brain Initiative

This interdisciplinary research effort pulls together faculty expertise, knowledge, and technical resources from across MIT to solve the mysteries of the aging brain. It spans neuroscience; fundamental biology and genetics; investigative medicine; engineering and computer science; economics; chemistry; urban planning; and artificial intelligence to enable a comprehensive systems approach.

What's the ultimate mission?
To deliver the foundational research that makes possible new tools to address the challenges of brain aging and create a better future for millions.

Support our Research

Faculty of the Aging Brain Initiative at MIT

Core MIT Members:

Ed Boyden, McGovern Institute for Brain Research, Media Lab, Departments of Biological Engineering and Brain & Cognitive Sciences; **Emery Brown**, Picower Institute for Learning and Memory, Department of Brain & Cognitive Sciences, and Anesthesia, Critical Care & Pain Medicine at Massachusetts General Hospital; **Leonard P. Guarente**, Department of Biology; **Robert Horvitz**, McGovern Institute for Brain Research and Koch Institute for Integrative Cancer Research, Department of Biology; **Manolis Kellis**, Computer Science and Artificial Intelligence Lab, Broad Institute, Department of Electrical Engineering & Computer Science; **Michael Sipser**, Past Dean of School of Science, Department of Mathematics; **Susumu Tonegawa**, Picower Institute for Learning & Memory, Departments of Brain & Cognitive Sciences and Biology; **Li-Huei Tsai**, Director, Aging Brain Initiative and Picower Institute for Learning & Memory

Collaborative MIT Members:

Mark Bear, Picower/BCS; **Gloria Choi**, Picower/BCS; **Joseph Coughlin**, Urban Planning, Engineering Systems; **Kwanghun Chung**, Picower/ChemE/IMES; **Peter Dedon**, Bio Eng; **Randall Davis**, EECS/CSAIL; **Ernest Fraenkel**, Bio Eng/CSAIL; **Steven Flavell**, Picower/BCS; **Linlin Fan**, Picower/BCS; **Ann Graybiel**, McGovern/BCS; **John Gabrieli**, McGovern/BCS/IMES; **Myriam Heiman**, Picower/BCS; **Thomas Heldt**, Bio Eng/EECS/IMES; **Alan Jasanoff**, McGovern/Bio Eng/BCS/Nuclear Science; **Ankur Jain**, Whitehead/Biology; **Rudolf Jaenisch**, Whitehead/Biology; **Laura Kiessling,** Chemistry; **Robert Langer**, ChemE/Bio Eng/Koch; **Andrew Lo**, Sloan/Finance; **Troy Littleton**, Picower/Biology; **Pattie Maes,** Media Lab; **Earl Miller**, Picower/BCS; **Tod Machover**, Media Lab; **Elly Nedivi**, Picower/BCS/Biology; **Sara Prescott**, Picower/Biology; **Ritu Raman**, Mech Eng; **Jean-Jacque Slotine**, Mech Eng/BCS; **Mriganka Sur**, Picower/BCS; **Steven Tannenbaum**, Bio Eng/Chemistry; **Joel Voldman**, EECS; **Giovanni Traverso,** Mech Eng, Brigham and Women's Hospital; **Matthew Wilson**, Picower/BCS/Biology; **Brady Weissbourd**, Picower/Biology; **Bin Zhang,** Chemistry

Thank you for investing in MIT talent – The Aging Brain Initiative Fund #3895642

The only way to decode the mysteries of the brain and to find a cure or better treatments for the dementias of aging—and to build on the momentum already created by the Aging Brain Initiative—is to support the innovation pipeline: the faculty, students, and other scientists engaged in fundamental brain aging research, and the tools and facilities that enable their work.

As we continue with this work and push forward to complete our next goals, we thank you for your support and hope you will consider renewing your support for the next year. A gift to our Aging Brain Initiative Fund can be made online by entering the fund number 3895642 on MIT's giving site: https://giving.mit.edu/. Unrestricted gifts to the ABI Fund supports priority needs across campus including seed and collaborative grants for launching new ideas into experiments, early human clinical studies, and a bi-annual symposium. To make a named or transformational gift, please contact Director of Development, **Dr. Asha Bhakar** at abhakar@mit.edu or 617-959-4385.