Aging Brain Initiative

NEWS 2024

/ Inside /

From the Director

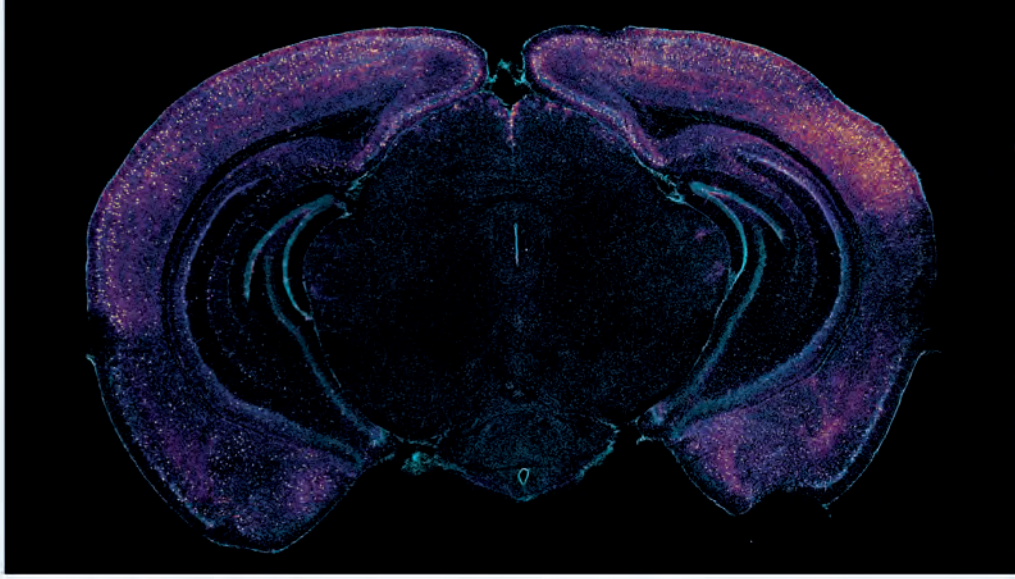
Dear Friends,

A fundamental distinction of MIT's Aging Brain Initiative is that we don't regard neurodegenerative diseases as just a neuroscience problem or a technology problem or a societal problem. Instead, we have been resolute from the beginning that MIT should address this urgent problem in a systemic, holistic fashion.

In this edition of our annual ABI newsletter, you can learn about many individual advances and insights (e.g. new candidate therapies, clinical studies, and technologies), but also take a moment to notice the breadth of the work that has occurred at MIT over the past year. It's encouraging and astonishing to see researchers ranging from linguists to engineers to computer scientists working on many aspects of the challenge. The research they're doing spans Alzheimer's disease and other dementias, ALS, Parkinson's disease and aging itself.

These efforts involve everyone from undergraduates to professors, but much of it is also because of your support. Thank you from all of us and thank you for reading.

Li-Huei Tsai,
Director, The Aging Brain Initiative



Alzheimer's proteins cleared via 'glymphatic' system

In *Nature*, MIT researchers showed that stimulating the brain with light and sound at 40 Hz promotes clearance of amyloid proteins, a hallmark of Alzheimer's pathology, via the brain's glymphatic system, a recently discovered "plumbing" network parallel to the brain's blood vessels.

The sensory stimulation increases the power and synchrony of gamma-frequency brain waves. In lab mice modeling Alzheimer's disease, that prompted a particular type of neuron to release "VIP" peptides that drove an increase in glymphatic fluid flows that can flush away amyloid. Former graduate student Mitch Murdock, co-supervised by Picower Professor **Li-Huei Tsai** and Y. Eva Tan Professor **Ed Boyden**, led the research.

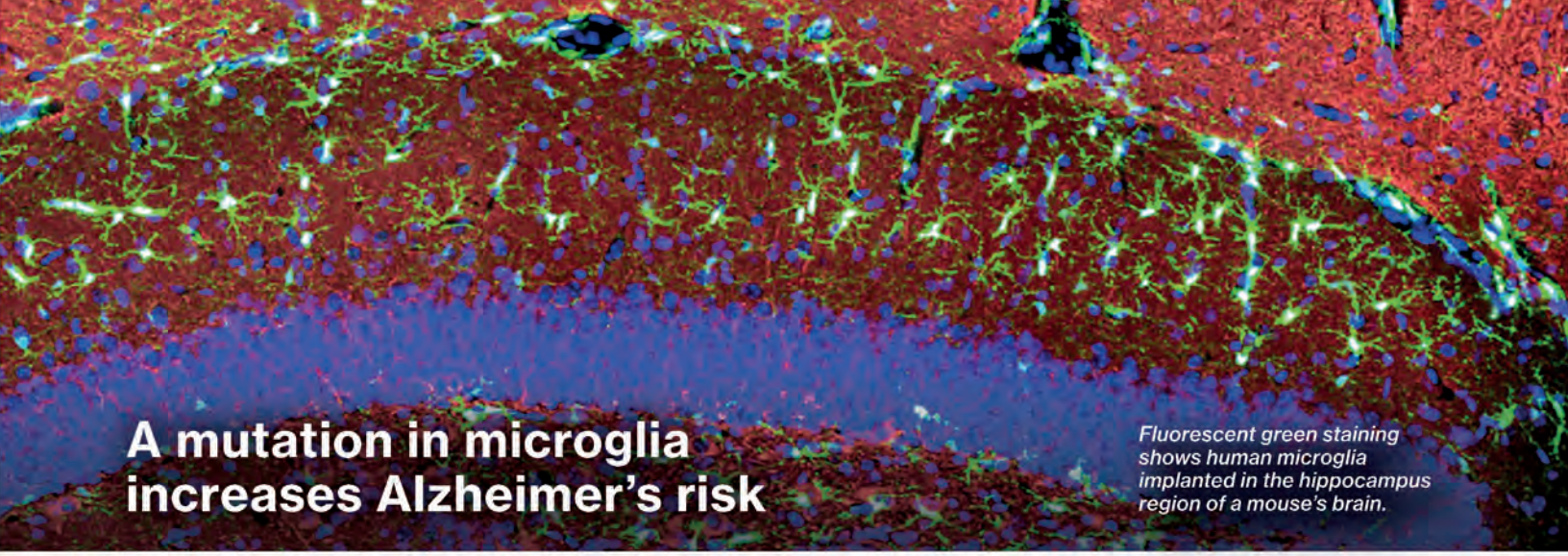
The team accumulated several lines of evidence of increased glymphatic fluid flow including increases in cerebrospinal fluid in the brain tissue of mice treated with 40 Hz sensory stimulation compared to untreated controls. They also measured an increase in the rate of interstitial fluid leaving the brain. Moreover, in the treated mice they measured increased diameter of the lymphatic vessels that drain away the fluids and measured increased accumulation of amyloid in cervical lymph nodes, which is the drainage site for that flow.

To investigate how this might be happening, the team focused on the aquaporin 4 (AQP4) water channel of astrocyte cells, which enables the cells to facilitate glymphatic fluid exchange. When they blocked APQ4 function with a chemical, that prevented 40 Hz stimulation from reducing amyloid levels and prevented it from improving mouse learning and memory. And when, as an added test, they used a genetic technique for disrupting AQP4, that also interfered with gamma-driven amyloid clearance.

In addition to the fluid exchange promoted by APQ4 activity in astrocytes, another mechanism by which gamma waves promote glymphatic flow is by increasing the pulsation of neighboring blood vessels. Several measurements showed stronger arterial pulsatility in mice subjected to 40 Hz gamma stimulation compared to untreated controls.

Further experiments showed that 40 Hz stimulation increased VIP release from neurons to drive these changes.

On the cover: Fluorescent staining highlights VIP-expressing interneurons in a cross-section of a mouse brain. The neurons may help drive glymphatic clearance of amyloid via the release of peptides.



A mutation in microglia increases Alzheimer's risk

Fluorescent green staining shows human microglia implanted in the hippocampus region of a mouse's brain.

In a study published in *GLIA*, first author Jay Penney, senior author Professor **Li-Huei Tsai** and co-authors discovered that a rare but potent mutation known as 'TREM2 R47H/+' leads to dysfunctional microglia in the brain. This microglial mutation had previously been associated with an increased risk for developing Alzheimer's disease, so it was important to pinpoint how it impacted cellular function.

The team employed CRISPR gene editing and human-induced pluripotent stem cells to gain insight into how the TREM2 R47H/+ mutation affected microglia. The mutant microglia were hyperresponsive to inflammatory challenges but were less likely to migrate over to injured neurons. When it came to clearing out harmful debris, including amyloid beta – the mutant microglia weren't doing their job.

By transferring the dysfunctional microglia into the brains of mice, they saw how the mutation led to overzealous microglia pruning back synapses between neurons, an impact that is likely to impair brain circuits and function. As the mechanisms underlying the microglial dysfunction become even more clear, drug developers can determine novel ways to target these cells in the case of TREM R47H/+ mutation.

Regional resilience and vulnerability to Alzheimer's disease

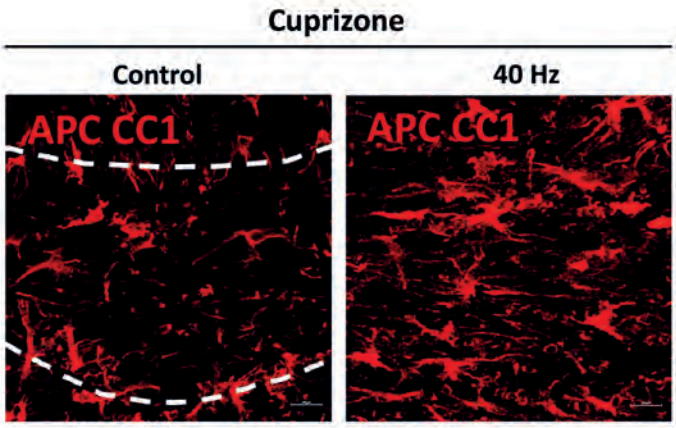
In *Nature*, co-senior authors **Manolis Kellis** and **Li-Huei Tsai** published a groundbreaking study dissecting Alzheimer's disease (AD) gene-by-gene and cell-by-cell across multiple regions of the brain. Hansruedi Mathys, Carles Boix and Leyla Akay led the investigation by analyzing data from six regions of the brain. Post-mortem samples were donated by 48 participants, 26 with an AD diagnosis, from the Religious Order Study or the Rush Memory and Aging Project of Rush University.

Because brain cells express their DNA it in different patterns, the group quantified gene expression in more than 1.3 million cells, allowing them to examine 70 different cell types from the six different regions of the brain. Tsai explained, "Specific brain regions are vulnerable in Alzheimer's and there is an important need to understand how these regions or particular cell types are vulnerable."

Kellis likened the methodology to a single-cell 'microscope' that "tells us cell by cell and gene by gene, about thousands of subtle yet important biological changes in response to pathology." The researchers were then able to connect the data to the cognitive condition of the patients in order to link specific genes and cell types to resilience or vulnerability to AD.

Specific types of excitatory neurons of the hippocampus and entorhinal cortex were less abundant in people with AD who had performed worse on cognitive tests. Of note, these cells exhibited much less expression of a protein called 'Reelin.' This protein has recently garnered attention in AD research, because researchers at the University of Antioquia and Mass General Hospital characterized a man with a rare mutation in the Reelin gene. He had a more active form of Reelin and was remarkably resilient to AD even though he was carrying other AD-related mutations. Another insightful finding was that across multiple regions of the brain, astrocytes expressing genes for antioxidant activity, choline metabolism and polyamine biosynthesis were associated with preservation of cognition – even when amyloid and tau were present at high levels.

"The dataset is so immensely rich. We focused on only a few aspects that are salient that we believe are very, very interesting, but by no means have we exhausted what can be learned with this dataset," Kellis said.



Red staining shows a higher abundance of myelinating oligodendrocyte cells in a brain region called the corpus callosum with 40Hz treatment (right).

40 Hz sensory stimulation protects myelin

A new study zeroes in on how 40 Hz sensory stimulation helps to sustain an essential process in which the signal-sending branches of neurons, called axons, are wrapped in a fatty insulation called myelin. Often called the brain's "white matter," myelin protects axons and insures better electrical signal transmission in brain circuits.

"Previous publications from our lab have mainly focused on neuronal protection," says Picower Professor **Li-Huei Tsai**. senior author of the paper in *Nature Communications*. "But this study shows that it's not just the gray matter, but also the white matter that's protected by this method."

In the new study, members of Tsai's lab led by former postdoc Daniela Rodrigues Amorim used a common mouse model of myelin loss – a diet with the chemical cuprizone – to explore how sensory stimulation preserves myelination.

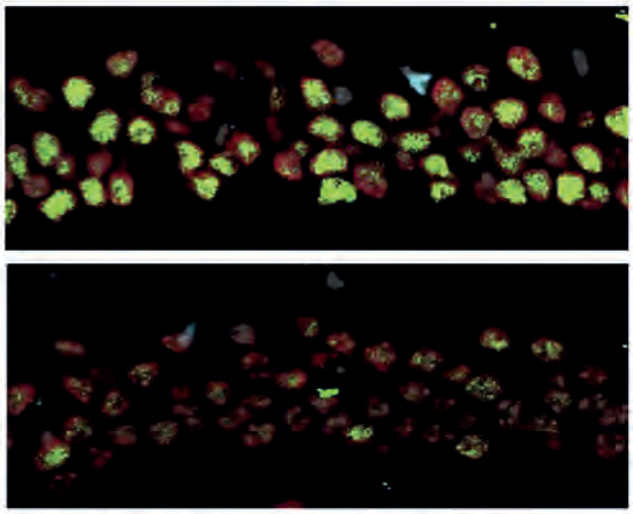
Amorim and Tsai's team found that 40Hz light and sound not only preserved myelination in the brains of cuprizone-exposed mice, it also appeared to protect oligodendrocytes (the cells that myelinate neural axons), sustain the electrical performance of neurons, and preserve a key marker of axon structural integrity. When the team looked into the molecular underpinnings of these benefits, they found clear signs of specific mechanisms including preservation of neural circuit connections called synapses; a reduction in a cause of oligodendrocyte death called "ferroptosis;" reduced inflammation; and an increase in the ability of microglia brain cells to clean up myelin damage so that new myelin could be restored.

Treating "chemo brain" non-invasively

Chemotherapy often leads to a frustrating condition known as "chemo brain," characterized by memory issues and difficulty concentrating. This year, a study led by TaeHyun Kim and ABI director **Li-Huei Tsai**, in *Science Translational Medicine*, explored the use of daily 40 Hz light and sound stimulation (GENUS) as a non-invasive treatment for the condition.

Mice exposed to daily 40 Hz therapy during chemotherapy treatment showed significant protection against damage caused by the common chemotherapeutic drugs cisplatin and methotrexate. These drugs can lead to inflammation in the brain, and the loss of white matter – tracts of nerve fibers wrapped in an insulating, fatty material called myelin. The protective benefits included reduced inflammation, preserved brain volume, and enhanced myelin production. Importantly, the mice performed better in behavioral tests designed to test short-term memory and executive function. Single-cell RNA sequencing revealed that GENUS suppressed inflammation and cell death-related genes, especially in oligodendrocytes, which are the cells critical for myelin production. Some of these beneficial effects could still be seen up to four months post-treatment.

Tsai notes: "Chemo brain caught our attention because it is extremely common, and there is quite a lot of research on what the brain is like following chemotherapy treatment. From our previous work, we know that this gamma sensory stimulation has anti-inflammatory effects, so we decided to use the chemo brain model to test whether sensory gamma stimulation can be beneficial."



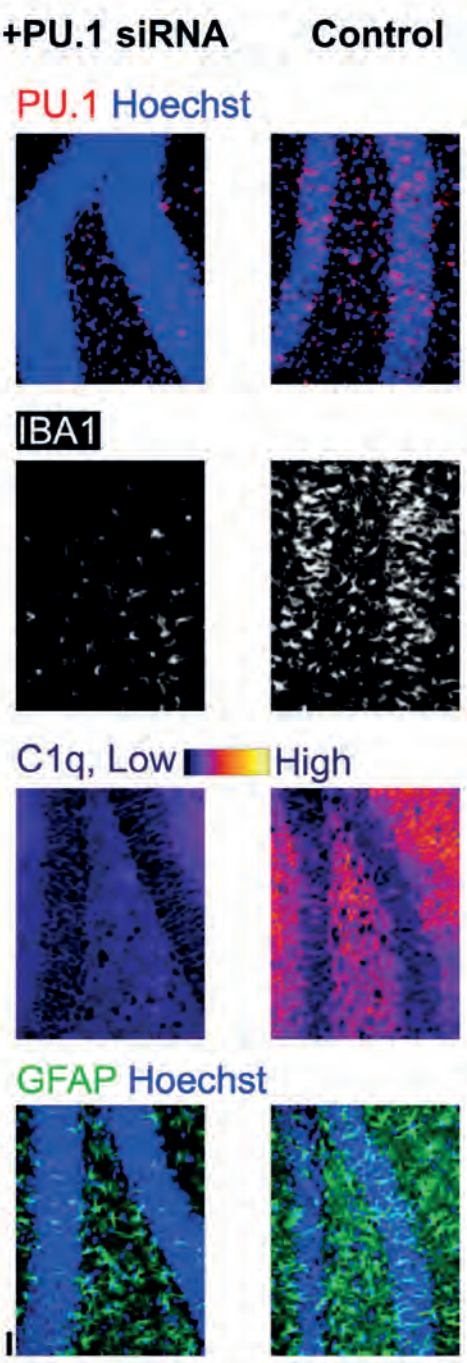
Mice treated with 40 Hz sensory stimulation (bottom) showed much less DNA damage (green) than mice that did not receive the stimulation (top) with chemotherapy.

Nanoparticles for neuroinflammation

Professor **Li-Huei Tsai** wanted a better way to deliver therapeutic, small interfering RNA (siRNA) to microglial cells in the brain. These cells have been hard to target, and their uncontrolled activation can result in inflammation that contributes to neurodegenerative disease. Her lab's prior work showed that blocking the actions of a protein known as PU.1, a regulator of errant microglia inflammation, helps to reduce Alzheimer's disease-related neuroinflammation and pathology. Tsai hypothesized that lipid nanoparticles (LNPs) could be used to facilitate delivery of siRNA targeting PU.1 into microglia, because these cells have a strong tendency to uptake lipid molecules. LNPs have been FDA-approved for use in other medicines, from cancer drugs to COVID-19 vaccines, so Tsai reached out to **Robert Langer**, David Koch Institute Professor, who is widely known for his pioneering work on nanoparticle drug delivery.

The team, which included graduate student Jason Andresen, former Tsai Lab postdoc William Ralvenius and co-lead author Owen Fenton of University of North Carolina, had to optimize an LNP for effective use with microglia. LNPs have four main components, so by changing the structures of two of them, and by varying the ratio of lipids to RNA, the researchers came up with multiple formulations to try in cultured mouse and human cells. One called 'MG-LNP' had an especially high delivery efficiency and safety profile. The researchers tested whether using MG-LNP to deliver a PU.1-targeting siRNA could reduce inflammation in microglia and found that a relatively low dose achieved an ideal level of PU.1 reduction without causing the cells any harm. In two mouse models of neuroinflammation, injection of MG-LNPs that carried anti-PU.1 siRNA as cargo was able to reduce expression of PU.1 and inflammatory markers in the mice.

Additional testing will be required before the idea could be tried in human patients, but Langer noted that this could potentially open new ways of treating certain brain diseases with nanoparticles in the future. The study was published in *Advanced Materials*.

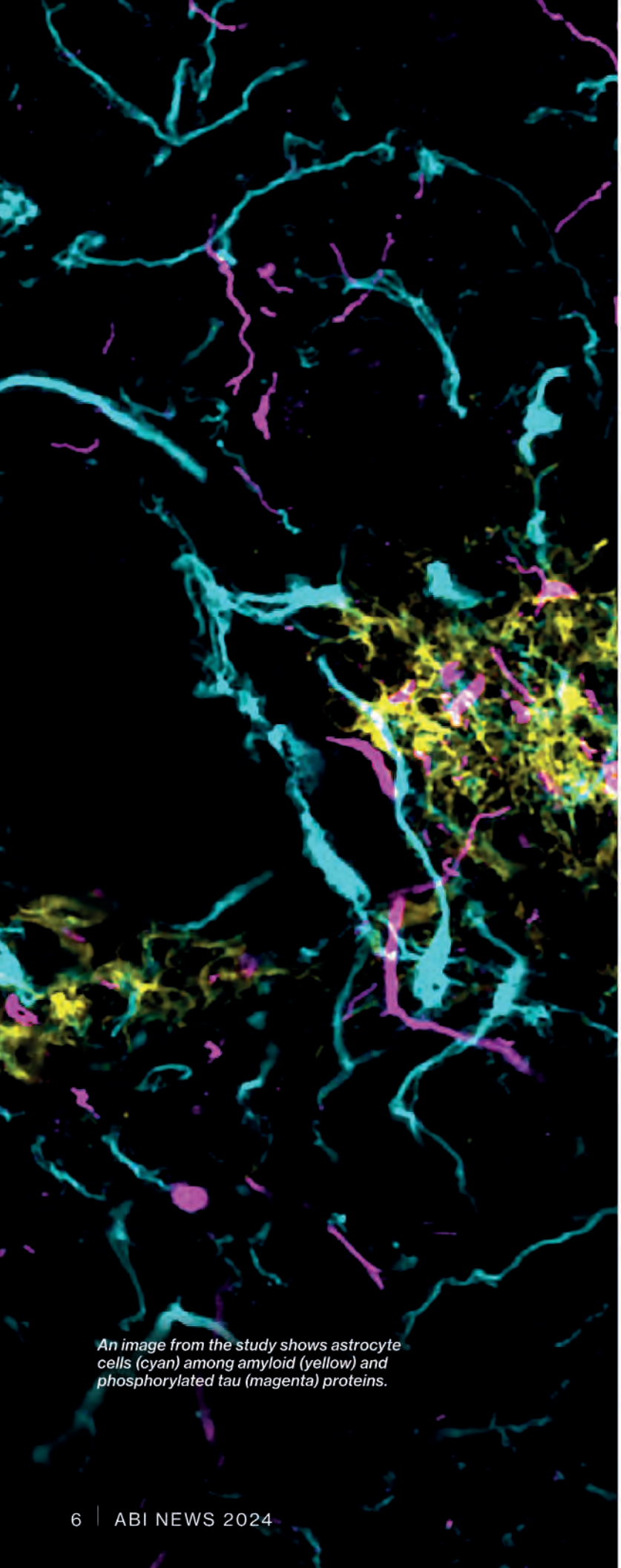


Results from an experimental control (right column) and the effects of the siRNA (left column). siRNA against PU.1 delivered by MG-LNP was able to reduce expression of PU.1 and related markers (IBA1, C1q, GFAP) in the brains of mice.

Watching cell signaling at work

Throughout the day, our cells have to respond to dynamic signals, from hormones to nutrients. The cells often respond with an intricate cascade of molecular events that drive cell function. Observing such responses over time can help researchers understand why cell function is lost in aging and disease. This past year in *Cell*, **Edward Boyden**, Y. Eva Tan Professor in Neurotechnology, and MIT postdoc Yong Qian reported a game-changing method for watching cell signaling at work. Before their invention, only two or three molecular responses could be reliably observed at a time, but now the researchers report real-time tracing of seven different molecules at a time.

To achieve this, they made use of green and red fluorescent molecules called 'switchable fluorophores,' which flicker on and off at different rates that are measurable with a microscope. With the help of a computational algorithm, they extracted each different fluorescent signal based on its flicker rate and calculated the amount and location of each of the molecules over time. Boyden's lab aims to adapt this elegant system for use in living mouse models in the future.



An image from the study shows astrocyte cells (cyan) among amyloid (yellow) and phosphorylated tau (magenta) proteins.

Method reveals new cells and structures in human brain tissue

Using a novel microscopy technique, MIT and Brigham and Women's Hospital/Harvard Medical School researchers have imaged human brain tissue in greater detail than ever before, revealing cells and structures that were not previously visible.

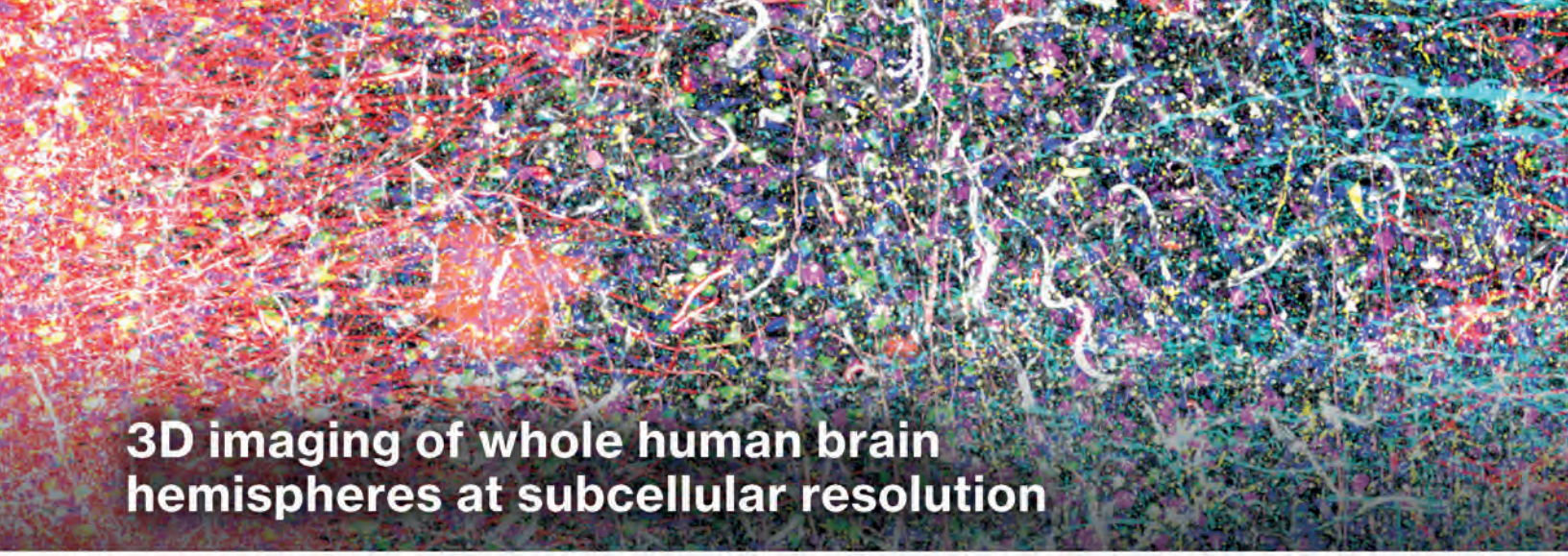
The new imaging method, co-led by **Edward Boyden**, Y. Eva Tan Professor in Neurotechnology, is based on expansion microscopy, a technique developed in Boyden's lab in 2015 with a simple premise: Instead of using powerful, expensive microscopes to obtain high-resolution images, the researchers devised a way to expand the tissue itself, allowing it to be imaged at very high resolution with a regular light microscope.

For this study, which demonstrated applications in human tissues for imaging cancer and Alzheimer's disease, the authors devised a different tissue-softening protocol that breaks up the tissue but preserves proteins in the sample. After the tissue is expanded, proteins can be labelled with commercially available fluorescent antibodies. The researchers then can perform several rounds of imaging, with three or four different proteins labeled in each round. This labelling of proteins enables many more structures to be imaged, because once the tissue is expanded, antibodies can squeeze through and label proteins they couldn't previously reach.

The researchers labeled up to 16 different molecules per tissue sample. The molecules they targeted include markers for a variety of structures, including axons and synapses, as well as markers that identify cell types such as astrocytes and cells that form blood vessels. They also labeled molecules linked to tumor aggressiveness and neurodegeneration.

Boyden's lab also plans to use this technique to study other aspects of brain function, in healthy and diseased tissue.

"Being able to do nanoimaging is important because biology is about nanoscale things — genes, gene products, biomolecules — and they interact over nanoscale distances," Boyden says. "We can study all sorts of nanoscale interactions, including synaptic changes, immune interactions, and changes that occur during cancer and aging."



3D imaging of whole human brain hemispheres at subcellular resolution

Observing anything and everything within the human brain while it is fully intact has been an out-of-reach dream of neuroscience for decades. But in *Science*, an MIT-based team describes a technology pipeline that enabled them to finely process, richly label, and sharply image full hemispheres of the brains of two donors — one with Alzheimer's disease and one without — at high resolution and speed.

"We performed holistic imaging of human brain tissues at multiple resolutions, from single synapses to whole brain hemispheres, and we have made that data available," said Associate Professor **Kwanghun Chung**. "This technology pipeline really enables us to analyze the human brain at multiple scales. Potentially this pipeline can be used for fully mapping human brains."

Chung collaborates with Matthew Frosch, an Alzheimer's researcher and director of the brain bank at Massachusetts General Hospital, to image and understand Alzheimer's disease brains. With the new pipeline they began an open-ended exploration, first noticing where within a slab of tissue they saw the greatest loss of neurons in the disease sample compared to the control. From there, they followed their curiosity — as the technology allowed them to do.

"We didn't lay out all these experiments in advance," Chung says. "We just started by saying, 'OK, let's image this slab and see what we see.' We identified brain regions with substantial neuronal loss so let's see what's happening there. We used many different markers to characterize and see the relationships between pathogenic factors and different cell types.

"This pipeline allows us to have almost unlimited access to the tissue," Chung says. "We can always go back and look at something new."

They focused most of their analysis in the orbitofrontal cortex within each hemisphere. One observation was that synapse loss was concentrated in areas where there was direct overlap with amyloid plaques. Outside of areas of plaques the synapse density was as high in the brain with Alzheimer's as in the one without the disease.

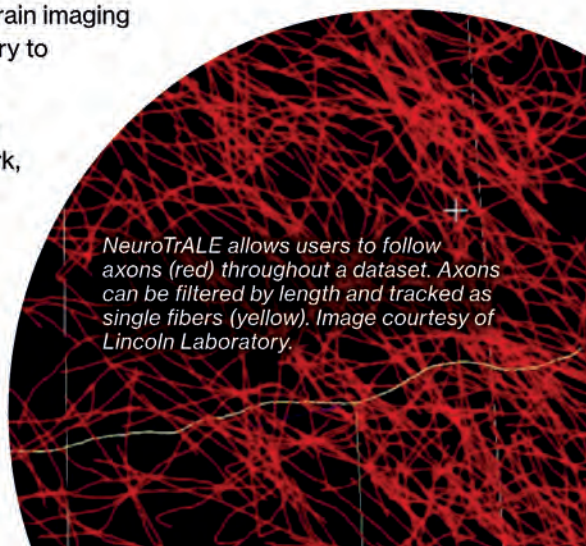
New open-source tool helps to detangle the brain

One of the key tools in **Kwanghun Chung**'s exploration of Alzheimer's brains was the Neuron Tracing and Active Learning Environment (NeuroTrALE) software developed at MIT Lincoln Laboratory by **Lars Gjesteby**, a technical staff member and algorithm developer. NeuroTrALE brings machine learning, supercomputing, and ease of use and access to brain mapping.

As part of their collaboration, Gjesteby's Lincoln team needed to build a way for Chung Lab researchers to analyze and extract useful information from their large amount of brain imaging data flowing into the MIT SuperCloud — a supercomputer run by Lincoln Laboratory to support MIT research.

NeuroTrALE automates much of the data processing and displays the output in an interactive interface that allows researchers to edit and manipulate the data to mark, filter, and search for specific patterns.

In 2020, the team uploaded NeuroTrALE to the SuperCloud and by 2022 the Chung Lab was producing results. In a study in *Science*, they used NeuroTrALE to quantify frontal cortex cell density in relation to Alzheimer's disease, where brains affected with the disease had a lower cell density in certain regions than those without. The same team also located where in the brain harmful neurofibers tend to get tangled in Alzheimer's-affected brain tissue.



NeuroTrALE allows users to follow axons (red) throughout a dataset. Axons can be filtered by length and tracked as single fibers (yellow). Image courtesy of Lincoln Laboratory.

Controlling unconsciousness

Anesthesia is an essential component of surgery, but it carries risks, especially for older patients. With a precise means to track and control the brain states of a patient, anesthesiologists could prevent cognitive side-effects by dialing in just the right level of unconsciousness. Most anesthesiologists are not trained to track brain states from electroencephalograms (EEGs), so they sometimes may administer anesthetic doses beyond what is needed.

Sophisticated feedback technology could circumvent this problem. That's just what **Emery Brown** and **Earl Miller** achieved with their teams at The Picower Institute for Learning and Memory and Massachusetts General Hospital in a study reported in *PNAS Nexus*. The research team, which included Sourish Chakravarty and Jacob Donoghue, developed a closed-loop anesthesia delivery (CLAD) system based on brain state monitoring, as well as the pharmacokinetics and pharmacodynamics of the anesthetic propofol. Their new CLAD system advances the field by achieving feedback control every 20 seconds for precise dosing. In an animal model, they were able to achieve more than 18 hours of fine-tuned consciousness control over the course of nine sessions. More work is needed to adapt the system to humans, but the authors have made a critical step forward.

Better sleep with brain wave technology

As we get older, we often experience changes in our sleep patterns and our ability to fall asleep. This can be frustrating, but in the near future, technology from the startup Elemind may help us get more rest. The company, which was founded by MIT Professor **Ed Boyden**, along with David Wang, Nir Grossman, Heather Read and Meredith Perry, has developed an electroencephalogram (EEG) headband with AI technology that measures brainwaves and accordingly emits sounds that can modulate brain waves in ways that promote sleep.

Elemind has begun a small pilot program and recently reported promising results from a small clinical trial in *Scientific Reports*. In adults with sleep onset insomnia, 30 minutes of sound stimulation from the device was able to reduce the amount of time it took participants to fall asleep. Elemind's CEO Perry noted, "We wanted to create a nonchemical option for people who wanted to get great sleep without side effects, so you could get all the benefits of natural sleep without the risks."

At McGill University, collaborators found that using the device during sleep increased activity in areas of the cortex involved in motor function and improved performance in memory tasks. Elemind is focused on their sleep application for now, but by establishing collaborations with several universities, the company sees a future of multiple uses for the technology.

Getting to the root cause of ALS

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a rare but fatal disease in which motor neurons progressively degenerate and impair essential muscle control. Pinpointing the causes of ALS has been difficult – some studies have pointed to genetic mutations that are associated with a higher risk but this isn't the complete picture. Epigenetic factors, which are modifications to DNA outside of the genetic code, may be at play.

In a recent study reported in *Nature Communications*, MIT scientists shed light on the epigenetics of ALS and discovered about 30 locations in the epigenome that were associated with the rate of disease progression in patients with ALS. The study was led by MIT Professor **Ernest Fraenkel** and MIT post-doc Stanislav Tsitkov.

As part of the Answer ALS consortium, the team analyzed epigenetic modifications in motor neurons derived from induced pluripotent stem cells from 380 individuals with ALS. In addition to the changes at 30 locations, they found a found a strong differential signal that associated with a specific subtype of ALS that is characterized by a genetic mutation in the C9orf72 gene. This information may help researchers develop targeted therapies for subtypes of ALS. Fraenkel reflected, "We may get to a point in a decade or so where we don't even think of ALS as one disease, where there are drugs that are treating specific types of ALS that only work for one group of patients and not for another."

Tsitkov explained that the team is now working to "...integrate the genomics, the transcriptomics, and the epigenomics, as a way to find subgroups of ALS patients who have distinct phenotypic signatures from other ALS patients and healthy controls."


Ernest Fraenkel

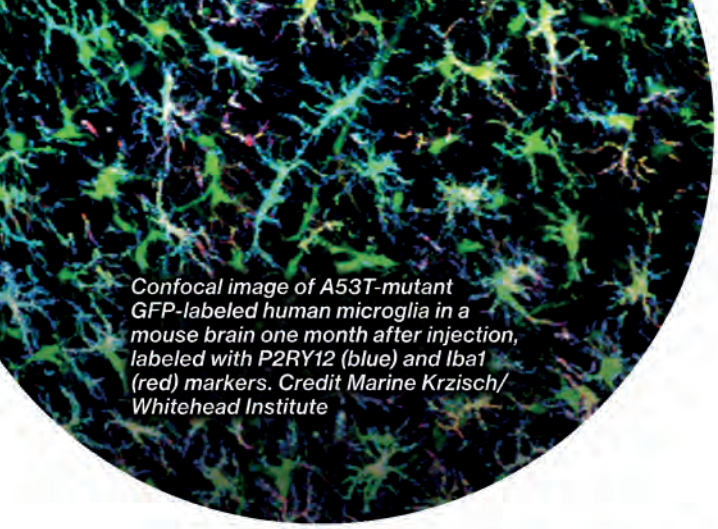
Convergence of ALS and FTLD

Amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) are both neurodegenerative disorders that share many pathological and genetic features. Yet, they affect patients in distinct ways; the former impacting muscles and movement and the latter impacting speech and behavior. To map out and better understand the two diseases, a new study led by researchers at MIT and the Mayo Clinic dug deeply into their cellular and molecular profiles and found striking overlap.

By measuring gene expression patterns in 620,000 cells from 44 different cell types in the motor cortex and prefrontal cortex from 73 donors, the research team was able to identify vulnerable cell types and molecular factors that may drive disease progression for both ALS and FTLD. The researchers also found overlapping gene expression patterns for inherited vs. sporadic forms of the disease, suggesting that even though the initial cause may be different, the diseases converge on similar pathways.

The study, published this year in *Cell*, was led by MIT graduate student Sebastian Pineda, co-senior authors **Myriam Heiman** and **Manolis Kellis** of MIT, and their collaborator Veronique Belzil previously of the Mayo Clinic and now at Vanderbilt University. Heiman noted that "These similarities were quite striking, suggesting that therapeutics for ALS may also apply to FTLD and vice versa."

Kellis reflected, "These common hallmarks can pave the path for a new modular approach for precision and personalized therapeutic development, which can bring much-needed new insights and hope."



Confocal image of A53T-mutant GFP-labeled human microglia in a mouse brain one month after injection, labeled with P2RY12 (blue) and Iba1 (red) markers. Credit Marine Krzisch/ Whitehead Institute

A new clue for understanding the molecular basis of Parkinson's

In a study in *Biological Psychiatry*, Whitehead Institute Founding Member **Rudolf Jaenisch** and former postdoctoral associate Marine Krzisch examine how a genetic mutation affects the resident immune cells of the brain called microglia. The mutation renders microglia extremely sensitive, worsening the problem of inflammation in the brain and potentially exacerbating damage to neurons in Parkinson's disease (PD).

"In fact, even when these mutant microglia are transplanted into a healthy, young [mouse] brain, they have heightened activation upon stimulation, and low levels of the protective antioxidant catalase," Krzisch says. "This tells us that in Familial Parkinson's disease, which is due to genetic mutations, these microglia may be playing an important role in neuron degeneration."

Scientists have identified more than 20 causative genes in which mutations can result in Familial PD, a rare, genetically inherited form affecting individuals under or around the age of 50. Among them is SNCA, which encodes for alpha-synuclein, a small protein abundant in dopamine-producing neurons.

The A53T mutation in SNCA promotes the formation of dysfunctional alpha-synuclein proteins that clump together within dopamine-producing neurons. The accumulation of these protein clumps, also known as Lewy bodies, triggers inflammatory signaling in the brain, eventually killing the affected neurons. Research has shown that the A53T mutation accelerates the progression of PD, or the rate at which neurons die.

The researchers compared the gene expression profiles of A53T-mutant microglia with those that did not carry the mutation, revealing differences in pathways linked to inflammation, microglia activation, and DNA repair. Additionally, when A53T-mutant microglia were exposed to an immune activator called lipopolysaccharide, they exhibited a heightened inflammatory response compared to non-mutant microglia. In fact, even in non-inflammatory conditions, A53T-mutant microglia had decreased expression of catalase, an enzyme that helps break down harmful reactive oxygen species produced in response to protein aggregates in PD.

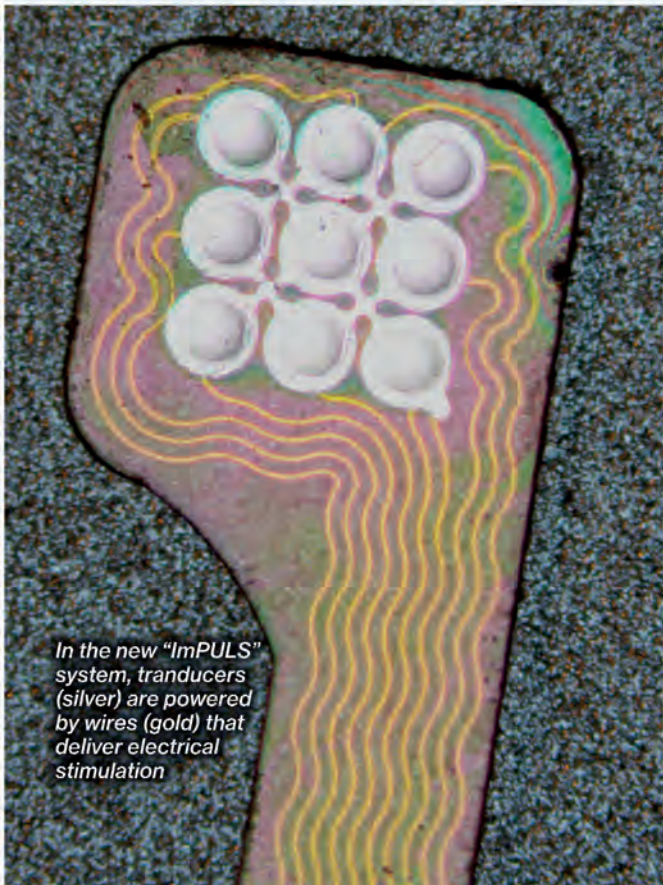
"Overactivation of microglia isn't the only cause of neuron death in Parkinson's," says Jaenisch. "But if we can decrease their activation, it will help us get to the point where we can slow down or actually stop the disease."

A new way to perform deep brain stimulation: Ultrasound

Deep brain stimulation, by implanted electrodes, is often used to treat Parkinson's disease (PD) and other neurological disorders. However, the electrodes can eventually corrode and accumulate scar tissue, requiring them to be removed.

MIT researchers have now developed an approach that uses ultrasound instead of electricity to perform deep brain stimulation, delivered by a fiber about the thickness of a human hair. In a study of mice, they showed that this stimulation can trigger neurons to release dopamine in a part of the brain that is often targeted in PD patients.

"By using ultrasonography, we can create a new way of stimulating neurons to fire in the deep brain," says **Canan Dagdeviren**, an associate professor in the MIT Media Lab and the senior author of the study in *Nature Communications*. "This device is thinner than a hair fiber, so there will be negligible tissue damage, and it is easy for us to navigate this device in the deep brain."



In the new "ImPULS" system, tranducers (silver) are powered by wires (gold) that deliver electrical stimulation

40 Hz spin-off company publishes Phase 2 clinical trial results

Cognito Therapeutics, the Cambridge startup company that has licensed MIT's 40Hz sensory stimulation technology, reported phase II clinical trial results in March showing safety and some significant clinical improvements in people with Alzheimer's disease.

More than 70 volunteers enrolled in Cognito's six-month "OVERTURE" trial of a headset that produces 40Hz flickering light and clicking sound. Patients used their headsets for an hour a day at home. The treatment proved safe for volunteers who adhered to treatment more than 85 percent of the time.

Patients didn't show improvement on every measure, but patients who received the active treatment rather than a placebo control showed significantly slowed declines on indices measuring daily functioning and cognition, and MRI measures of brain volume. Treated participants showed a 76 percent lower decline on the Mini Mental State Exam, which tests five areas of cognitive function, for example.

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

Clinical studies in aging epigenetics

The Aging Research Center of Elysium Health, co-founded by ABI core member **Leonard Guarente**, is currently enrolling participants in two landmark clinical studies: 1) the 'Translational Initiative to Map Epigenetics in Aging' (TIME-A) and 2) the 'Translational Initiative to Map Epigenetics in Sleep' (TIME-ZZZ) to advance our understanding of the connections between epigenetics, lifestyle factors and biological aging over time.

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. More details here: picower.mit.edu/support/volunteer

Participate in MIT Research

Evidence emerging that 40 Hz stimulation can treat neurological disorders

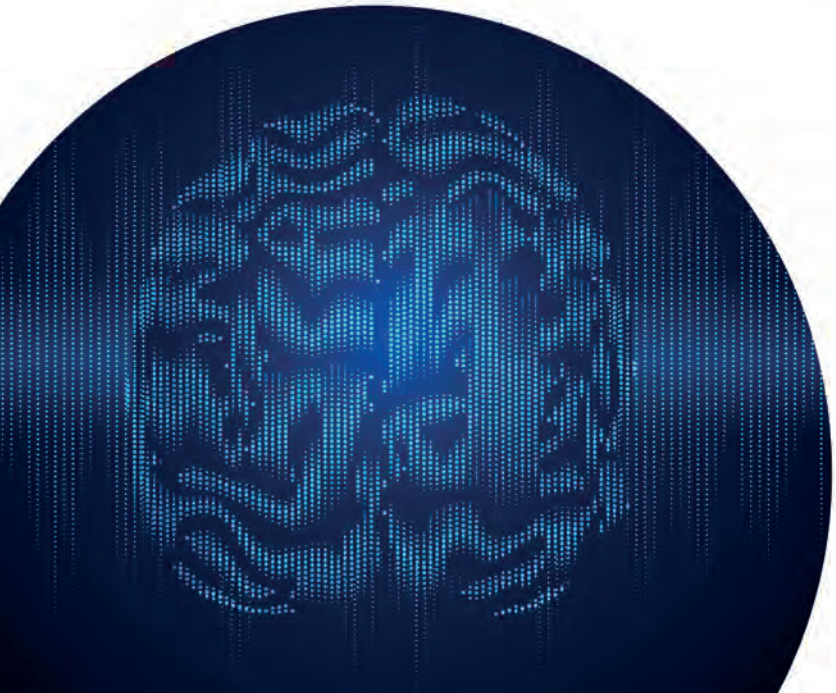
A surprising MIT study in 2016 spurred interest in the possibility that stimulating the 40 Hz gamma-band brain rhythm could produce meaningful therapeutic effects for people with Alzheimer's disease. In a review paper in the *Journal of Internal Medicine*, the lab that led those studies provided an overview of what a growing number of scientists worldwide have been finding out since then in dozens of clinical and lab benchtop studies.

"What started in 2016 with optogenetic and visual stimulation in mice has expanded to a multitude of stimulation paradigms, a wide range of human clinical studies with promising results, and is narrowing in on the mechanisms underlying this phenomenon," write the authors including Picower Professor **Li-Huei Tsai**.

Though the number of studies and methods has increased and the data have typically suggested beneficial clinical effects, the article's authors also clearly caution that the clinical evidence remains preliminary and that animal studies intended to discern how the approach works have been instructive, but not definitive.

"Research into the clinical potential of these interventions is still in its nascent stages," the researchers, led by former MIT postdoc Cristina Blanco-Duque, wrote. "The precise mechanisms underpinning the beneficial effects of gamma stimulation in Alzheimer's disease are not yet fully elucidated."

Still, the authors summarized early but promising results from 16 clinical studies published over the last several years. They also examined dozens more studies investigating underlying mechanisms in lab animals.



Making sense of sentences before dementia

The use of 'cognitive biomarkers,' such as subtle changes in language processing, could aid clinicians in detecting and treating Alzheimer's disease (AD) earlier. To capture these changes, MIT Professor **Suzanne Flynn** and collaborators at Cornell and Mass General Hospital, tested people with the amnestic subtype of mild cognitive impairment (aMCI). Individuals with aMCI are at an increased risk of developing dementia due to AD. When working with complex sentences, people with aMCI performed significantly worse than control groups when producing sentences with 'anaphoric coreference' - in linguistics terms, this means that the sentences have ambiguity about the identity of the person referred to by a pronoun. For example, "The plumber fixed the drain when he visited the tenant," it is not entirely clear if 'he' refers to the plumber, or somebody else who happened to be visiting that day. Individuals with aMCI had not lost the ability to process syntax or put complex sentences together, but a subtle deficit was revealed when they had to work with an ambiguous pronoun.

Flynn noted: "This adds to our understanding of the deterioration that occurs in early stages of the dementia process. Deficits extend beyond memory loss. While the participants we studied have memory deficits, their memory difficulties do not explain our language findings, as evidenced by a lack of correlation in their performance on the language task and their performances on measures of memory. This suggests that in addition to the memory difficulties that individuals with aMCI experience, they are also struggling with this central aspect of language."

The study was published earlier this year in the *Journal of Neurolinguistics*.

AgeLab PLAN forum looks at future of longevity planning

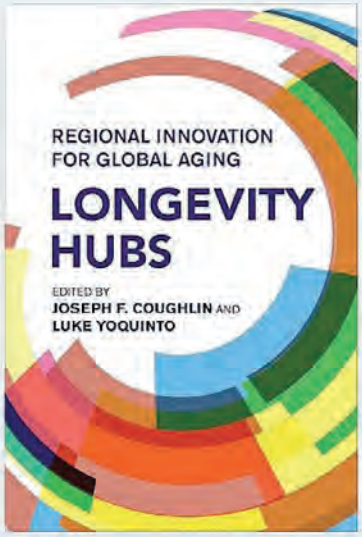
Longevity planning is the transformation of the financial services and retirement planning industries into a holistic business of advice and services to help people navigate a 100-year lifespan. A two-day symposium at MIT in May highlighted how new technologies, changing consumer preferences, and increasing life expectancy will shift the financial advisory profession into this new industry.

Hosted by the Preparing for Longevity Advisory Network (PLAN), a research consortium of MIT's AgeLab directed by Professor **Joseph Coughlin**, the event featured speakers including Karen Lynch, CEO of CVS, and Penny Pennington, managing partner at Edward Jones as well as experts from other industries such as real estate.

The second day of the symposium focused on new technologies that have potential to guide longevity planning. Virtual reality, artificial intelligence, and health prediction technologies, among others, are tools that can help people imagine and predict their futures. Each panel was accompanied by a reflection session of financial advisors, who discussed how these new technologies might impact their industry.

Professor **Li-Huei Tsai**, director of the ABI, discussed the potential of genetic testing to identify patients' predispositions toward Alzheimer's disease. Alzheimer's disease, which remains without a cure, could be better managed if identified as a risk earlier in life. Rita Shaknovich, vice president of medical affairs at Grail Inc., a health diagnostic company, discussed the development of technologies that can detect cancer at early stages through a blood test, with the aim of rendering the "emperor of maladies" a manageable chronic condition instead of an often fatal one.

A later panel focused on applications of artificial intelligence in medicine and health care and its implications for other industries.



New book examines 'Longevity Hubs'

A new MIT Press book due out Nov. 19 examines innovation hotspots for the world's aging population.

Edited by Professor **Joseph Coughlin**, director of MIT's AgeLab, and Research Associate Lucas Yoquinto, "Longevity Hubs: Regional Innovation for Global Aging" brings together essays by a variety of experts who explore how specific regions will soon distinguish themselves as longevity hubs: homes to disproportionate economic and innovative activity for older populations.

Longevity Hubs opens on Greater Boston, with the collected articles comprising the "Longevity Hub" special project that ran in the Boston Globe in 2021 and 2022, including one by ABI Director **Li-Huei Tsai**. Then the book zooms out to look at Longevity Hubs around the nation and world.

Maiken Nedergaard takes questions from the audience moderated by symposium host Li-Huei Tsai.

MIT's Aging Brain Initiative Symposium

Presenters at MIT's ABI Symposium in late 2023 delivered an exciting sampling of research on neurodegenerative diseases such as Alzheimer's and ALS. The symposium was entitled "Cutting Edge Approaches to Studying the Aging Brain" where hundreds of people gathered at Building 46 and online from 21 countries.

The symposium featured a keynote from University of Rochester Professor Maiken Nedergaard, a ground-breaking neuroscientist who discovered the brain's "glymphatic system." This system is essential for healthy brain function as it removes old proteins from brain tissue. However, its effectiveness declines with aging. "It's clear that the brain has a major problem with waste clearance, because the diseases of aging, the neurodegenerative diseases, can all be regarded as diseases of a dirty brain," Nedergaard said.

The next ABI Symposium will be hosted as a full-day event, entitled, "**The Neuro-Immune Axis and the Aging Brain**." Please join us on Thursday, **September 18, 2025** at the Picower Institute for Learning and Memory for a full day of talks and a poster session exploring the neuro-immune axis and the aging brain with a keynote delivered by Michal Schwartz of the Weizmann Institute of Science.

Gilliam Fellowship supports MIT graduate student

With support from the Howard Hughes Medical Institute (HHMI) Gilliam Fellows Program, graduate student **Mingus Rae Zoller** has begun exciting Alzheimer's disease (AD) research at MIT. Zoller's project in Professor **Li-Huei Tsai**'s lab aims to advance our understanding of AD, with a particular focus on immune cells, including microglia, macrophages and T cells in the brain. She will examine the intersecting roles of TREM2 mutations, immune cells and brain activity, and will then test 40Hz stimulation as a potential therapy to target immune dysregulation.

The work is personal for Zoller whose father has been unexpectedly diagnosed with AD. Her family has no history of AD nor clear cause to point to. "This is the biggest mystery of my life. How did my dad get Alzheimer's disease?" Zoller expressed. "If I can contribute one tiny bit of information to explain how AD progresses or how someone could get it, that would be personally fulfilling. That's a big driving force for me."

The Gilliam fellowship will also provide Zoller and Tsai with resources to promote diversity, equity and inclusion. Zoller noted "Diversity is not just a moral imperative; it's essential for scientific excellence, as diverse teams are generally found to be more innovative and effective at solving complex problems."

“La Caixa” Foundation ABI fellows

To accelerate the Aging Brain Initiative’s research and advance innovative therapies, “la Caixa” Foundation in Spain established postdoctoral fellowships at MIT. The current “la Caixa” Foundation ABI fellows are **Tamara Rossy** and **Fábio Garrudo** – two innovative scientists who are flourishing in the MIT environment. Rossy is working with Assistant Professor **Ritu Raman** in the Department of Mechanical Engineering to develop an advanced in vitro model of the neuromuscular interface in order to study the pathogenic mechanisms underlying amyotrophic lateral sclerosis (ALS). Her in vitro system will allow her to model and closely examine exercise’s impact and potential as a therapy for ALS and other neurodegenerative diseases. Garrudo works with MIT Professor and ABI Director **Li-Huei Tsai** and is developing brain-on-chip models on bioengineered surfaces that can provide precise stimulations and real-time measurements of cell health and interactions. His innovation will facilitate drug-screening and advance our mechanistic understanding of Alzheimer’s disease.


Tamara Rossy


Fábio Garrudo

Notable honors for ABI members:

Emery N. Brown, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience in The Picower Institute for Learning and Memory, was elected to the 2023 class of members of the American Philosophical Society.

Steve Flavell, Associate Professor in The Picower Institute for Learning and Memory and the Department of Brain and Cognitive Sciences at MIT, has been named a Hughes Medical Institute (HHMI) Investigator.

Linlin Fan, Assistant Professor in The Picower Institute for Learning and Memory and the Department of Brain and Cognitive Sciences, has been named as a Klingenstein-Simons Fellow.

Elly Nedivi, William R. (1964) & Linda R. Young Professor of Neuroscience in The Picower Institute for Learning and Memory, was named the 2023 recipient of the Krieg Cortical Kudos Discoverer Award by the Cajal Club.

Sara Prescott, Assistant Professor in the Department of Biology and The Picower Institute for Learning and Memory at MIT, has been named as a Pew Scholar.

Brady Weissbourd, Assistant Professor in the Department of Biology and The Picower Institute for Learning and Memory, has been named as a Searle Scholar.

Heiman lab looks to learning the secrets of neural longevity

Neurons in the brain can live for more than 90 years, making them exceptional examples of longevity among cells, but scientists know little about how neurons achieve that long lifespan. With a new Glenn Foundation Discovery Award, Associate Professor **Myriam Heiman** and her group plan a research project that will expand on preliminary work aimed at discovering the genetic and molecular basis of neural longevity.

Support from the award, $525,000 over three years from the Glenn Foundation for Medical Research and the American Federation for Aging Research will enable Heiman’s lab to conduct rigorous and unbiased testing in the mammalian nervous system to discover genes that sustain neural longevity.

“The mechanisms that underlie the exceptional longevity of nerve cells in our brain remain unclear,” Heiman said. “If they were understood, however, they could be targeted to restore nerve cell function in the context of aging and neurodegeneration, and they could also potentially be induced in other cell types of the body to increase the healthspan of the whole organism.”


Myriam Heiman

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; **Robert Langer**, ChemE/Bio Eng/Koch; **Andrew Lo**, Sloan/Finance; **Troy Littleton**, Picower/Biology; **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; **Matthew Wilson**, Picower/BCS/Biology; **Brady Weissbourd**, Picower/Biology

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.