Aging Brain Initiative

NEWS 2023

Human studies of 40 Hz sensory stimulation confirm safety, suggest Alzheimer's benefits

Early-stage clinical studies testing the safety and efficacy of 40 Hz sensory stimulation to treat Alzheimer's disease has found that the potential therapy was well-tolerated, produced no serious adverse effects, and was associated with some significant neurological and behavioral benefits among a small cohort of participants. Results appeared in *PLOS ONE*.

One set of tests, which enrolled 43 volunteers of various ages, including 16 people with early-stage Alzheimer's, confirmed that exposure to 40 Hz light and sound was safe and that it increased 40 Hz rhythm and synchrony after a few minutes of exposure, as measured with EEG electrodes. The study, led by the lab of Picower Professor and Aging Brain Initiative director **Li-Huei Tsai**, also included two patients at the University of Iowa who consented to having measurements taken in deeper brain structures during exposure to 40 Hz sensory stimulation while undergoing epilepsy-related surgery.

The second set of tests enrolled 15 people with early-stage Alzheimer's disease in a single-blinded, randomized, controlled study to test exposure to 40 Hz light and sound for an hour a day for at least three months. Volunteers used the stimulation device (a light panel synchronized with a speaker) in their homes.

The eight volunteers treated with 40 Hz stimulation experienced several beneficial effects that reached statistical significance compared to the seven volunteers in the control condition. Control participants exhibited two signs of brain atrophy as expected with disease progression: reduced volume of the hippocampus and increased volume of open spaces, or ventricles. Treated patients did not experience significant changes in these measures. Treated patients also exhibited better connectivity across brain regions involved in the brain's default mode and medial visual networks, which are related to cognition and visual processing respectively. Treated patients also exhibited more consistent sleep patterns than controls.

Treated patients also fared significantly better than controls on a face-name association memory test.

40Hz vibrations fight Alzheimer's in mice

Evidence that noninvasive sensory stimulation of 40 Hz gamma frequency brain rhythms can reduce Alzheimer's disease (AD) pathology and symptoms, already shown with light and sound by multiple research groups in mice and humans, now extends to tactile stimulation. A new study in *Frontiers in Aging Neuroscience* led by the lab of Picower Professor **Li-Huei Tsai** shows that Alzheimer's model mice exposed to 40 Hz vibration for an hour a day for several weeks showed improved brain health and motor function compared to untreated controls.

Among mice modeling AD, those stimulated with vibration for three weeks showed significant preservation of neurons compared to unstimulated controls and showed significant reductions in harmful tau tangles. Among mice who modeled AD in a different way, treatment reduced levels of DNA damage and increased levels of synaptic protein markers compared to in unvibrated controls.

Both mouse models, if they received 40 Hz vibration treatment, performed better on motor tests. For instance, they were able to stay on a rotating rod significantly longer.

On the cover: Former graduate student Brennan Jackson helps a 40 Hz study participant into the MRI for a brain scan.

From the Director

Dear Friends,

When we established the Aging Brain Initiative eight years ago our sense was that the complexities of neurodegeneration were not going to yield to a narrow approach. Instead we sought to bring the best of MIT together with a far-reaching call to action that would recruit everyone—engineers, computer scientists, chemists, physicians, economists—who had a contribution to make to what is not only a problem of biology, but also of technology and society.

We have made a great deal of progress in that time, though so much more needs to be done and the urgency has only increased. In the pages that follow you'll find many examples of advances across MIT in fundamental science, therapeutic approaches and technology development that are each encouraging in their own right. But what amazes me is what they show in the aggregate. Most of these studies are the products of collaborations among multiple labs, multiple disciplines, and in some cases, multiple institutions.

All this research activity is a strong sign that interest is building across MIT to address the many dimensions of dementia. It didn't happen just because of us. Your support has been instrumental. We thank you for your interest and for reading.

All the best during the upcoming holidays,

Li-Huei Tsai, *Director, The Aging Brain Initiative*

Decoding the complexity of Alzheimer's disease

Researchers tracking gene expression amid Alzheimer's discovered important changes in the brain's microglia immune cells (red).

To discover new Alzheimer's treatment targets, MIT researchers have performed the broadest and most detailed analysis yet of the genomic, epigenomic, and transcriptomic changes that occur in major cell types in the brains of Alzheimer's patients. The results appeared in four back-to-back papers in *Cell* in September.

Using more than 2 million cells from 427 postmortem brain samples, the researchers analyzed how gene expression is disrupted as Alzheimer's progresses. They also tracked changes in cells' epigenomic modifications, which help to determine which genes are turned on or off in a particular cell.

The studies were led by Picower Professor **Li-Huei Tsai**, director of the Aging Brain Initiative, and **Manolis Kellis**, a professor of computer science and a core ABI member. Their findings suggest that an interplay of genetic and epigenetic changes feed on each other to drive the pathological manifestations of the disease.

"It's a multifactorial process," Tsai said. "These papers together use different approaches that point to a converging picture of Alzheimer's where the affected neurons have defects in their 3D genome, and that is causal to a lot of the disease phenotypes we see."

The team analyzed patterns of how 54 types of brain cells each express genes and identified cellular functions that were most affected in Alzheimer's patients. Among the most prominent, they found impairments related to mitochondrial function, synaptic signaling, which governs how well neurons communicate, and maintaining the structural integrity of the genome. They also found that genetic pathways related to lipid metabolism were highly disrupted.

The analysis also revealed that cognitively resilient people had larger populations of two subsets of inhibitory neurons in the prefrontal cortex.

Another paper revealed that every type of cell in the brain undergoes a phenomenon known as "epigenomic erosion" as Alzheimer's progresses, meaning that the cells'

normal pattern of accessible genomic sites is lost, which contributes to loss of cell identity.

In a third paper, the researchers used RNA sequencing to classify microglia into 12 different states, based on hundreds of genes that are expressed at different levels during each state. They showed that as Alzheimer's progresses, more microglia enter inflammatory states. The Tsai lab is now exploring ways to activate implicated transcription factors, in hopes of treating Alzheimer's by programming inflammation-inducing microglia to switch back to a homeostatic state.

In the fourth paper the researchers examined how DNA damage contributes to the development of Alzheimer's. As more DNA damage accumulates in neurons, it becomes more difficult for them to repair the damage, leading to rearrangements of DNA and 3D folding defects. Repair mistakes also lead to a phenomenon known as gene fusion, which occurs when rearrangements take place between genes, leading to dysregulation of genes. Alongside defects in genome folding, these changes appear to predominantly impact genes related to synaptic activity, likely contributing to the cognitive decline seen in Alzheimer's disease as neurons struggle to transmit information in brain circuits.

Li-Huei Tsai and Manolis Kellis discuss their research with a colleague.

Molecule reduces inflammation in Alzheimer's models

In a new study, MIT scientists describe a candidate drug that in human cell cultures and Alzheimer's mouse models reduced inflammation and improved memory.

The target of the new "A11" molecule is a genetic transcription factor called PU.1. Prior research has shown that amid Alzheimer's disease, PU.1 becomes an overzealous director of inflammatory gene expression in the brain's microglia immune cells. A11 suppresses this problematic PU.1 activity, the new study in the *Journal of Experimental Medicine* shows, by recruiting other proteins that repress the inflammatory genes PU.1 works to express. But because A11 concentrates mostly in the brain and does not reduce PU.1 levels, it does not appear to disrupt PU.1's other job, which is to ensure the production of a wide variety of blood cells.

The team screened more than 58,000 small molecules from libraries of FDA-approved drugs and novel chemicals to see if any could safely and significantly reduce key inflammation and Alzheimer's-related genes regulated by PU.1 in cell cultures. After several rounds of increasingly stringent screening, they narrowed the field down to six chemicals. A11 was by far the most potent among them.

"Inflammation is a major component of Alzheimer's disease pathology that has been especially hard to treat," says study senior author **Li-Huei Tsai**, Picower Professor of Neuroscience and director of MIT's Aging Brain Initiative. "This preclinical study demonstrates that A11 reduces inflammation in human microglia-like cells, as well as in multiple mouse models of Alzheimer's disease, and significantly improves cognition in the mice. We believe A11 therefore merits further development and testing."
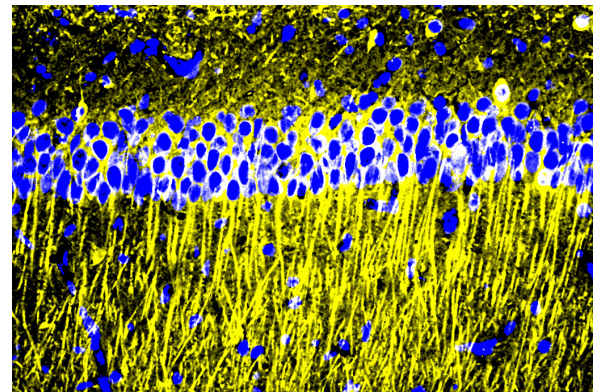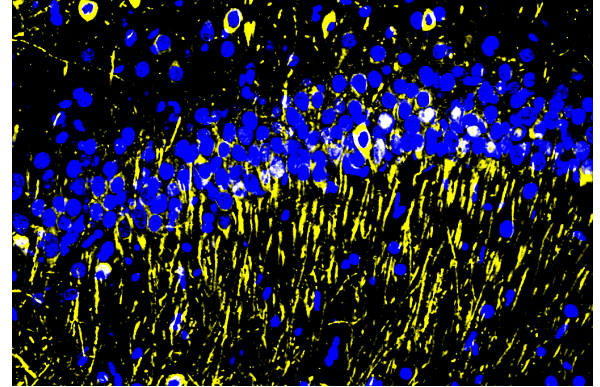
The brains of Alzheimer's model mice treated with A11 (bottom) showed more tubulin (yellow), a marker of neuronal health, than untreated controls (top).

Atlas of human brain blood vessels highlights changes in Alzheimer's disease

In a new study, Aging Brain Initiative researchers characterized gene expression patterns for 22,500 brain vascular cells across 428 human brain donors, revealing insights for Alzheimer's onset and potential treatments.

The analysis, published in *Nature Neuroscience*, revealed 2,676 genes whose expression levels change significantly in Alzheimer's brains. Scientists led by ABI Core Member **Manolis Kellis** and ABI director **Li-Huei Tsai** found that capillary endothelial cells, responsible for transport, waste removal, and immune surveillance, showed the most changes in AD, including genes involved in clearance of amyloid beta, one of the pathological hallmarks of AD.

Other dysregulated processes included immune function, glucose homeostasis, and extracellular matrix organization, which were all shared among multiple vascular cell types. Changes in specific cell types included growth factor receptors in pericytes, and transporter and energy in endothelial cells, and cellular response to amyloid beta in smooth muscle cells. Regulation of insulin sensing and glucose homeostasis in particular suggested important connections between lipid transport and Alzheimer's regulated by the vasculature and blood-brain-barrier cells, which could hold promise for new therapeutic approaches.

Neuroscientists identify cells especially vulnerable to Alzheimer's

One of the first brain regions to show neurodegeneration in Alzheimer's disease (AD) is a part of the hypothalamus called the mammillary body. In a new study, MIT researchers have identified a subset of neurons there that are most susceptible to neurodegeneration and hyperactivity. They also found that this damage leads to memory impairments.

The findings suggest that this region may contribute to some of the earliest symptoms of Alzheimer's disease, making it a good target for potential new drugs, say the researchers led by Picower Professor and Aging Brain Initiative Director **Li-Huei Tsai**.

In the study in *Science Translational Medicine*, the researchers showed they could reverse memory impairments caused by hyperactivity and neurodegeneration in mammillary body neurons by treating mouse models with levetiracetam, an epilepsy drug.

To learn more about the mammillary body's function, the researchers used single-cell RNA-sequencing, which can reveal the genes that are active within different types of cells. The sequencing identified two major populations of neurons: one in the medial mammillary body and the other in the lateral mammillary body. In the lateral neurons, genes related to synaptic activity were very highly expressed, and the researchers also found that these neurons had higher spiking rates than medial mammillary body neurons. Further experiments showed that the lateral neurons were more vulnerable to AD.
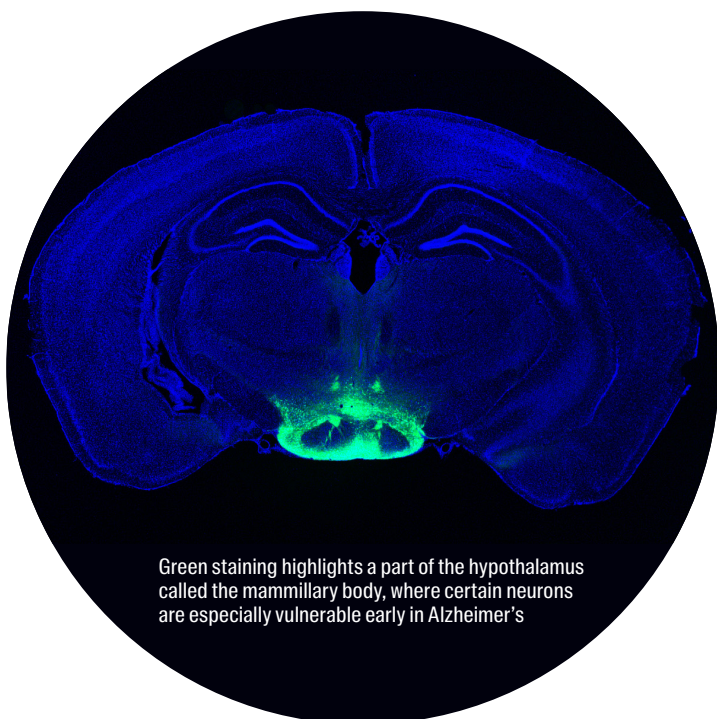
Green staining highlights a part of the hypothalamus called the mammillary body, where certain neurons are especially vulnerable early in Alzheimer's

New peptide may hold potential as an Alzheimer's treatment

MIT neuroscientists have found a way to reverse neurodegeneration and other symptoms of Alzheimer's disease by interfering with an enzyme that is typically overactive in the brains of Alzheimer's patients.

When the researchers treated mice with a peptide that blocks the hyperactive version of an enzyme called CDK5, they found dramatic reductions in neurodegeneration and DNA damage in the brain. These mice also showed improvements in their ability to perform memory tasks such as learning to navigate a water maze.

With further testing, the researchers hope that the peptide could eventually be used as a treatment for patients with Alzheimer's disease and other forms of dementia that have CDK5 overactivation. The peptide does not interfere with CDK1, an essential enzyme that is structurally similar to CDK5, and is similar in size to other peptide drugs that are used in clinical applications.

CDK5 is normally activated by a smaller protein known as P35. In Alzheimer's and other neurodegenerative diseases, P35 is cleaved into a smaller protein called P25, which can also bind to CDK5 but has a longer half-life than P35.

When bound to P25, CDK5 becomes more active in cells. P25 also allows CDK5 to phosphorylate molecules other than its usual targets, including the Tau protein. Hyperphosphorylated Tau proteins form the neurofibrillary tangles that are one of the characteristic features of Alzheimer's disease.

The MIT team led by Picower Professor and Aging Brain Initiative Director **Li-Huei Tsai** designed their peptide with a sequence identical to that of a segment of CDK5 that is critical to the binding of CDK5 to P25 so it blocks that binding.
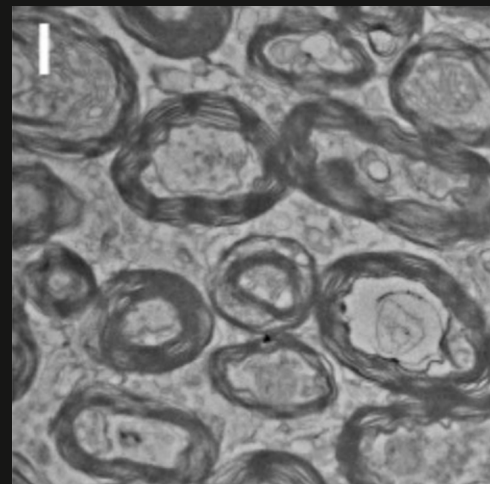
The study appeared in the *Proceedings of the National Academy of Sciences*.

A material called myelin forms a sheath around the long axon projections that extend from neurons. In these cross sections the myelin is much thicker in people with the APOE3 gene variant.
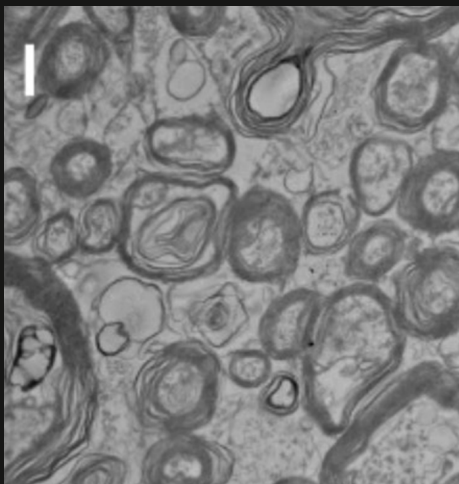
APOE 4/4

APOE 3/3

Alzheimer's risk gene undermines insulation of brain's "wiring"

Carrying the APOE4 version of APOE gene is the biggest genetic risk factor for Alzheimer's disease. Several recent studies from the lab of Picower Professor and Aging Brain Intiative Director **Li-Huei Tsai** have shown that errant lipid metabolism is a major factor.

For instance, a study in *Nature* combined evidence from postmortem human brains, lab-based human brain cell cultures, and Alzheimer's model mice to show that when people have one or two copies of APOE4, rather than the more common and risk-neutral APOE3 version, cells called oligodendrocytes mismanage cholesterol, failing to transport the fat molecule to wrap the long vine-like axon "wiring" that neurons project to make brain circuit connections.

Deficiency of this fatty insulation, called myelin, may be a significant contributor to the pathology and symptoms of Alzheimer's because without proper myelination, communications among neurons are degraded.

The study presented the first systematic analysis across major brain cell types using single nucleus RNA sequencing (snRNAseq) to compare how gene expression differs in people with APOE4 compared to the more typical and harmless APOE3 version. The analysis showed that APOE4-carrying oligodendrocytes exhibited greater expression of cholesterol synthesis genes and disruptions to cholesterol transport. The more APOE4 copies people had, the greater the effect.
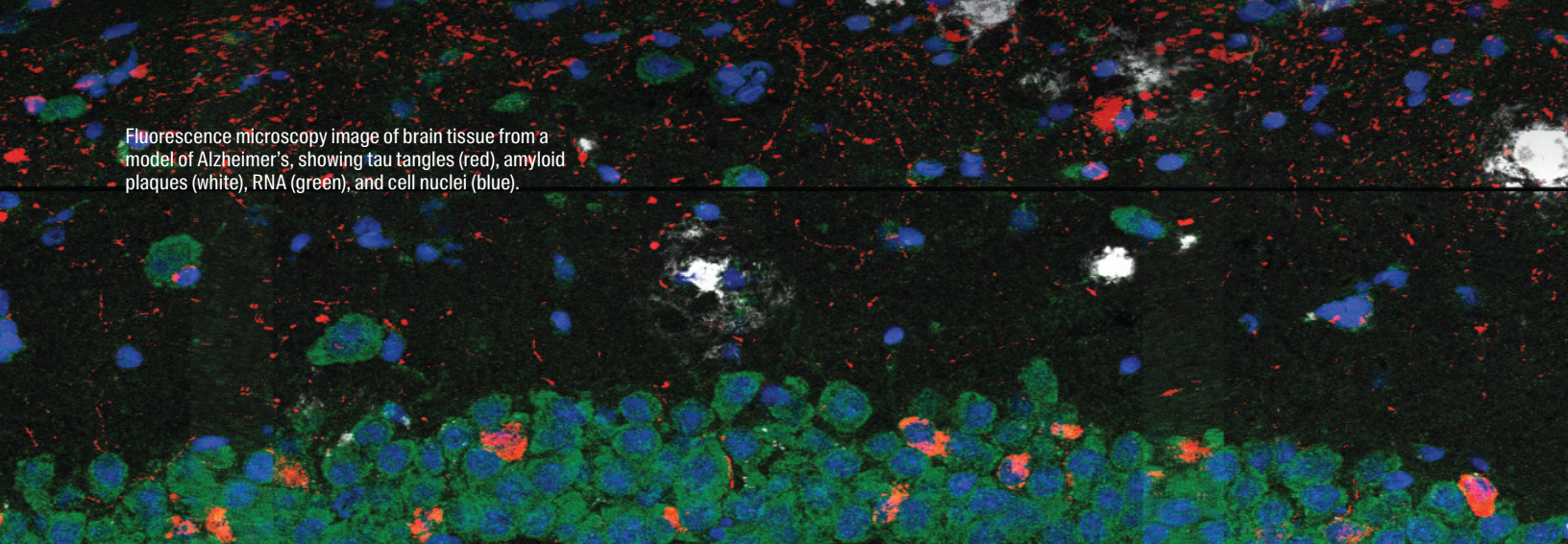
Eager to find a potential intervention, the team focused on drugs that affect cholesterol, including statins (which suppress synthesis) and cyclodextrin, which aids cholesterol transport. The statins didn't help, but applying cyclodextrin to APOE4 oligodendrocytes cultured in a dish reduced accumulation of cholesterol within the cells and improved myelination in co-cultures with neurons. Moreover, it also had these effects in APOE4 mice.

Trial explores choline's effects for APOE4 carriers

Choline is an essential nutrient found in foods like meat, eggs, and dairy. Studies in the lab of Picower Professor and Aging Brain Initiative Director **Li-Huei Tsai** have shown that it can counteract the disruptive effects of the APOE4 Alzheimer's risk allele on the lipid profile of astrocyte brain cells, helping to preserve their ability to support neuronal functions.

In APOE4 mice, a high-choline diet decreased neuroinflammation and Alzheimer's related brain pathology. This June, MIT and MD Anderson in Houston started a clinical trial at UTHealth to explore the effects of six months of dietary choline supplementation on the lipid profile in the blood and cerebrospinal fluid (CSF) of asymptomatic APOE4 carriers. The goal is to identify blood or CSF lipids that are dysregulated in APOE4 carriers and altered with a high-choline diet. These biomarkers will then be used to select the most suitable participants for a larger, placebo-controlled trial that will use brain scans to assess the effects of choline supplementation on brain pathology.

Fluorescence microscopy image of brain tissue from a model of Alzheimer's, showing tau tangles (red), amyloid plaques (white), RNA (green), and cell nuclei (blue).

Researchers map brain cell changes in Alzheimer's

In a study in *Nature Neuroscience*, Broad Institute researchers led by MIT Professor **Morgan Sheng** used a new method they developed to reveal how brain cells located near the Alzheimer's hallmark proteins amyloid-β and tau tangles change as the disease progresses in a mouse model.

Differences in gene expression of cells surrounding the proteins give scientists a clearer picture of how cells respond to the protein deposits in the brain — insights that could one day help scientists evaluate existing Alzheimer's treatments and develop new ones. For instance, the scientists found that processes such as the brain's inflammatory response and the differentiation of glial cells such as in microglia immune cells were connected to disease progression.

How Tau tangles form in the brain

In the healthy brain, Tau proteins bind to microtubules and help to stabilize them, but many neurodegenerative diseases, including Alzheimer's, are characterized by tangled proteins called Tau fibrils. In a new study in *Science Advances*, MIT chemistry professor **Mei Hong** and co-authors report new insight into how these fibrils form, and identified a potential target for drugs that could interfere with this formation.

The researchers pinpointed a sequence of amino acids that appears to help the Tau protein bend in different directions, which they believe could make a good target for drugs that would interfere with the formation of Tau tangles.

Estrogen decline may explain women's higher Alzheimer's risk

Scientists at Scripps Research and MIT have found a clue to a molecular cause of Alzheimer's that may explain why women are at greater risk.

In *Science Advances* the researchers showed that a chemically modified form of an inflammatory immune protein called complement C3 was present at much higher levels in the brains of women who had died with the disease compared to men who had died with the disease.

Complement proteins can trigger brain-resident immune cells called microglia to destroy synapses—the connection points through which neurons send signals to one another. Loss of synapses is a correlate of cognitive decline in Alzheimer's brains.

Estrogen can have brain-protective effects under some conditions. The researchers hypothesized that estrogen specifically protects women's brains from C3 modification—and this protection is lost when estrogen levels fall sharply with menopause. Experiments with cultured human brain cells supported this hypothesis. C3 modification increased as estrogen (β-estradiol) levels fell, due to the activation of an enzyme. This increase in modified C3 activated microglial destruction of synapses.

Steven Tannenbaum, Underwood-Prescott Professor of Biological Engineering at MIT, collaborated with Scripps Professor Stuart Lipton on the study.

Emery N. Brown

Anesthesiologists must monitor many aspects of a patient's condition during surgery. A new index could help them prevent patients from falling into too deep a state of unconsciousness.

Tracking brain waves could reduce post-op complications

When patients undergo general anesthesia, their brain activity often slows down as they sink into unconsciousness. Higher doses of anesthetic drugs can induce a deep state of unconsciousness known as burst suppression, which is associated with cognitive impairments after the patient wakes up.

A new study in the *Proceedings of the National Academy of Sciences,* in which the researchers analyzed the EEG patterns of patients under the anesthesia drug propofol, has revealed brain wave signatures that could help anesthesiologists determine when patients are transitioning into burst suppression. This could enable them to prevent patients from falling into that state, reducing the risk of postoperative brain dysfunction.

In burst suppression, EEG recordings from the brain show long periods of inactivity, punctuated by brief bursts of low-amplitude oscillations. Patients in this state are more likely to experience postoperative confusion, delirium, and memory loss. These effects, which can last for hours, days, weeks, or months, are more common in elderly patients.

One of these distinctive patterns tracked in the new study emerged in the brain's alpha waves (which have a frequency of eight to 14 cycles per second). Once patients became unconscious, these waves started to wax and wane in amplitude. As patients went deeper into unconsciousness, the pattern of this waxing and waning, or amplitude modulation, continually changed.

"If you track this modulation as it gets deeper or shallower, you have a very principled way to track level of unconsciousness under anesthesia," says core Aging Brain Initiative member **Emery N. Brown**, the Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience.

The researchers hypothesize that propofol exerts these effects through its influence on neuron metabolism.

"This is consistent with the observation that burst suppression is very frequent in older patients because their metabolic state may be less well-regulated than that of younger patients," Brown says.

Researchers improve cognition assay

Clinicians often assess patients with age-related cognitive impairments using a pen-and-paper maze. The test, however, can fail to elicit distinct indications of different disorders. Professor **Randall Davis** of MIT's Computer Science and Artificial Intelligence Laboratory is developing a better, digital version.

The "dMaze" uses a digitizing pen that tracks not only total maze completion time but also overall, maximum, and median speed and speed at critical choice points in the maze. In initial testing among participants with healthy cognition, mild cognitive impairment (MCI), Alzheimer's or Parkinson's disease, the dMaze's statistics resolved significant differences among the conditions.

Healthy volunteers, for instance, tend to complete the maze relatively quickly without a fast maximum speed, while MCI patients tend to hurry at critical choice points without finishing any more quickly.

"Relative speed differences for more complex choices may be sensitive to preclinical cognitive change even when total completion time is not," Davis and co-author Dana Penney of Beth Israel Lahey Hospital conclude in the journal *Alzheimer's & Dementia.*

How Huntington's disease affects different neurons

In patients with Huntington's disease, neurons in a part of the brain called the striatum are among the hardest hit. Neuroscientists at MIT have now shown in *Nature Communications* that two distinct cell populations in the striatum are affected differently by Huntington's disease.
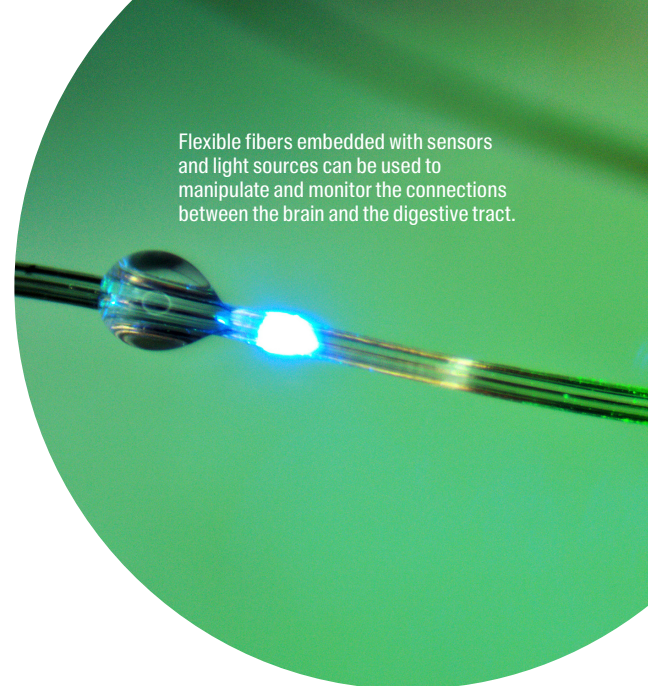
The findings suggest that neurodegeneration within structures called the striosomes, which are known to be involved in regulating mood, may be responsible for the mood disorders that strike Huntington's patients in the early stages of the disease. Later on, degeneration of the neurons in a structure called the matrix likely contributes to the decline of motor function, the researchers say.

Using single-cell RNA sequencing to analyze the genes expressed in mouse models of Huntington's disease and postmortem brain samples from Huntington's patients, the researchers found that cells of the striosomes and the matrix begin to lose their distinguishing features as the disease progresses. The researchers hope that their mapping of the striatum and how it is affected by Huntington's could help lead to new treatments that target specific cells within the brain.

"This study addresses an important outstanding question in the field, how striosome-matrix striatal projection neuron identity is affected in Huntington's disease," said study co-senior author **Myriam Heiman**, an associate professor in The Picower Institute for Learning and Memory. "The use of single-cell RNA profiling has allowed us to address this question for the first time in a comprehensive manner."

This kind of analysis could also shed light on other brain disorders that affect the striatum, such as Parkinson's disease and autism spectrum disorder, the researchers say.

Along with Heiman, who is an affiliate member of the Aging Brain Initiative, the study's other co-senior authors are MIT Institute Professor **Ann Graybiel**, also an affiliate ABI member, and computer science Professor **Manolis Kellis**, a core ABI member.

Myriam Heiman

Ann Graybiel

Manolis Kellis

Flexible fibers embedded with sensors and light sources can be used to manipulate and monitor the connections between the brain and the digestive tract.

New tech can probe circuits linking gut to brain

The brain and the digestive tract are in constant communication, relaying signals that help to control feeding and other behaviors.

MIT engineers have designed a new technology for probing those connections. Using fibers embedded with a variety of sensors, as well as light sources for optogenetic stimulation, the researchers have shown that they can control neural circuits connecting the gut and the brain in mice.

In a new study in *Nature Biotechnology*, the researchers demonstrated that they could induce feelings of fullness or reward-seeking behavior in mice by manipulating cells of the intestine. In future work, they hope to explore some of the correlations that have been observed between digestive health and neurological conditions such as autism and Parkinson's disease.

Polina Anikeeva, the Matoula S. Salapatas Professor in Materials Science and Engineering and Brain and Cognitive Sciences is the study's senior author.

Actor Chris Hemsworth dons AGNES for an episode of the TV show "Limitless with Chris Hemsworth"

"We use AGNES to give researchers and students a taste of the friction, frustration, and fatigue that older adults often experience"

Professor Joe Coughlin, director of AgeLab and an Aging Brain Institute affiliate member.

Suit helps people better understand aging

A suit called AGNES is an empathy and research tool designed by the MIT AgeLab to simulate for the wearer some of what it may feel like to live in one's early 80s with a few chronic health conditions.

Embedded weights approximate muscle loss, bungies the reduction of range of motion and flexibility that can affect the joints with age. Foam-platform Crocs simulate the erosion of balance, and heavy, awkward gloves evoke the loss of tactile sensation. Red goggles simulate a range of impairments to vision, from impaired acuity to diabetic retinopathy.

AGNES helps designers, engineers, executives, and others understand the physical and social world of older people so that they can design better products and services for them. It has been used globally to inform the design of public transportation systems, retail environments, medical devices, and product packaging.

"We use AGNES to give researchers and students a taste of the friction, frustration, and fatigue that older adults often experience," said Professor **Joe Coughlin**, director of AgeLab and an Aging Brain Institute affiliate member.

AGNES appeared in a documentary series titled "Limitless with Chris Hemsworth," produced by National Geographic and streamed on Disney+. The series was directed by Darren Aronofsky ("Noah," "Black Swan") and starred actor Chris Hemsworth.

Early in the episode, Hemsworth complained about wearing AGNES — "this suit sucks, by the way" — and attempted to overcome its limitations by brute effort. He lost a game of ping pong and exhausted himself in an aerobics class. But by the second day of wearing the suit, he realized that there was no way for him to defy the limits that AGNES brings. Instead, he begins to learn how to adapt to them and finally to accept them, and to allow himself to depend more on other people.

MIT spinoff advances 40 Hz research

The MIT discovery that non-invasive sensory stimulation at the 40 Hz gamma frequency may treat Alzheimer's disease requires pivotal human clinical testing on a scale typically achieved in the commercial sector. *Cognito Therapeutics*, a company founded by Aging Brain Initiative core member **Ed Boyden**, Y Eva Tan Professor of Neurotechnology, and ABI Director **Li-Huei Tsai**, Picower Professor of Neuroscience, made several research and logistical advances toward that goal in 2023.

In March the company announced it had raised $73 million from venture investors. The company said the funding will advance its pivotal Phase III HOPE for Alzheimer's Disease clinical trial, in which it is currently enrolling 500 patients across approximately 50 clinical centers in the United States.

At AD/PD, a major research conference in April, the company announced phase II trial data indicating that 40 Hz stimulation decreases brain atrophy in Alzheimer's patients. Compared to 28 control patients, 46 who received treatment exhibited significantly reduced loss of whole brain volume as measured by MRI. Then in July at the Alzheimer's Association International Conference (AAIC), the company revealed another phase II trial analysis finding that gamma sensory stimulation therapy reduced the decline in white matter/grey matter (WM/GM) contrast in the entorhinal region of the brain, which is affected especially early in disease.

Participate in MIT Research

Rebecca Pinals' research builds on the Tsai Lab's miBrain research platform, an integrated cell culture model of the human brain, integrating all the major types of brain cells within a network of blood vessels. Here a yellow astrocyte clings to a magenta blood vessel.

Rebecca Pinals

Postdoc earns Burroughs Wellcome Fund award

Picower Institute postdoctoral fellow **Rebecca Pinals** is among nine winners of the *Burroughs Wellcome Fund's 2023 Career Awards at the Scientific Interface*.

The awards recognize "exceptional researchers whose work exemplifies the collaborative spirit necessary for breakthrough discoveries," according to BWF's announcement. Pinals and the other winners will each receive a five-year, $500,000 grant supporting their research.

In the lab of Picower Professor **Li-Huei Tsai**, Pinals is creating a nanosensor-integrated human "brain-on-a-chip" culture of multiple cell types to enable novel studies of neurodegeneration. Combining tiny sensors into more realistic brain-like tissue modeling Alzheimer's could improve understanding of how the disease gains its terrible hold on the brain.

"I believe this research will be transformative in providing insight into the earliest stages of neurodegenerative disease dynamics, toward identifying key nodes in disease progression at which we can effectively intervene and, ultimately, prevent this devastating disease," Pinals said. "More broadly, I aim to co-develop nano-tools that operate at high spatiotemporal resolution, together with tractable neuro-models that more accurately recapitulate features of the human brain, to open new avenues of research in neurobiology."

Pinals said she is grateful for the award's support and the help she's had along the way as she looks to set up her own lab in the future.

"I am foremost grateful, and completely ecstatic to receive this recognition!" Pinals said. "This funding will help me through a critical transition from my postdoctoral position into my independent career as faculty. I am incredibly grateful to all of my mentors, colleagues, friends, and family who helped me get to this point."

MIT remembers Richard Wurtman, 86

Richard Wurtman, the Cecil H. Green Distinguished Professor Emeritus and a member of the MIT faculty for 44 years, died Dec. 13, 2022. He was 86.

In 1967, MIT invited him to start a neurochemistry and neuropharmacology program in the Department of Nutrition and Food Science. In the early 1980s he joined the newly formed Department of Brain and Cognitive Sciences.

"Dick Wurtman was a pioneer in studying the role of neurotransmitters in the brain, and neuroendocrine regulation of normal and abnormal brain function," says Newton Professor of Neuroscience **Mriganka Sur**. "His work on the impact of nutrition on neurotransmitters such as acetylcholine and on neuronal membrane synthesis laid the groundwork for later translational work on brain diseases such as Alzheimer's disease."

Picower Professor **Li-Huei Tsai**, director of the Aging Brain Initiative added: "His nutrient clinical trial work and establishment of the MIT Clinical Research Center have been tremendously helpful for my own work on understanding how high doses of supplement choline could potentially help reduce certain Alzheimer's risk, and our team's development of clinical studies at MIT to test Alzheimer's therapies."

Richard Wurtman

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:

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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.