

# Aging Brain Initiative

**NEWS 2021**

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**Choline may mitigate  
Alzheimer's risk**

**New Alzheimer's  
risk genes ID'd**

**New Parkinson's,  
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Massachusetts  
Institute of  
Technology

## Memory-making means DNA-breaking



*To express the genes we need for memory and learning – and do it quickly – a new study shows that brain cells snap open their DNA in many more places and cell types than we thought. Over time this breakage could cause cognitive decline.*

For the brain to remember a dangerous experience, neurons and other brain cells break open both strands of DNA to get fast access to the instructions needed to store these memories.

Double strand breaks (DSBs) are generally easy to repair, but the repair process can become more flawed and fragile with age, says **Li-Huei Tsai**, Director of MIT's Aging Brain Initiative (ABI) and the Picower Institute, who led the new study in *PLOS One*. Tsai's lab showed that repair mechanisms can falter and that lingering DSBs can be associated with neurodegeneration.

When they created a fear memory in mice and then assessed their DSBs and gene expression, researchers found that the fear memory doubled the number of DSBs. And when they looked at non-neuronal brain cells, or glia, they found that changes in hundreds of genes also occurred after fear conditioning.

Many of the glial DSBs occurred at genomic sites related to glucocorticoid receptors, which are involved in stress response. Directly stimulating those receptors could trigger the same DSBs that fear conditioning does, and blocking the receptors could prevent the transcription of genes after fear conditioning.

This suggests that glia may have a much larger role to play in the response to stress and its impact on the brain during learning.

## As novel sights become familiar, different neurons and brain rhythms take over



*To focus on what's new, we disregard what's not. A new study by ABI Affiliate **Mark Bear**'s Picower Institute lab increases our understanding of how our brains form this "visual recognition memory."*

"It's essential for normal brain function to make a quick determination of whether a stimulus is novel or not," says Bear. "If you learn that a once-novel stimulus isn't anything of significance, it's adaptive to no longer pay attention to it." People with schizophrenia and some autism spectrum disorders appear to struggle with this capability.

The study in the *Journal of Neuroscience* suggests that as visual recognition memory emerges in the visual cor-

tex, the neurons in charge of the memory change: as novel visual patterns become familiar, one circuit of inhibitory neurons takes over from another, and slower neural rhythms prevail.

Specifically, high-frequency gamma rhythms give way to lower-frequency beta rhythms, and the activity of the neurons that produce gamma rhythms declines. This brain rhythm shift is an externally measurable indicator of the move from novel to familiar.

Bear's lab is working with Boston Children's Hospital to determine if this frequency transition can be used as an early biomarker of autism spectrum disorders.

## Neuroscientists identify brain circuit that encodes event timing

*For every new event we experience, our brains record a memory of not just what happened, but when and where.*

A study from ABI Core member Susumu Tonegawa's lab found how the timing of a memory is encoded in the hippocampus and suggests that time and space are encoded separately.

The study in the *Proceedings of the National Academy of Sciences* identified a hippocampal circuit in mice used to store timing information (for instance, when it was the correct run through the maze to turn left). The findings add to growing evidence that when we form new memories, time and place information is encoded by different neurons.

An important aspect of the work is the idea that spatial and temporal information can operate in parallel and might merge or separate at different points in the circuit, depending on what we need to accomplish when we recall memory.

## Choline supplements may help APOE4 gene carriers

### Study links gene to cognitive resilience in the elderly

*Many people develop Alzheimer's disease or other forms of dementia as they age, while others stay sharp well into old age – even if their brains show underlying signs of neurodegeneration.*

Research has already shown that people who lead enriching lives are less prone to Alzheimer's disease and age-related dementia: Enrichments like education level and time spent on intellectually stimulating activities help prevent dementia among these cognitively resilient people.

Now, a new study from ABI Director Li-Huei Tsai's lab, shows these enriching activities seem to activate a gene family called MEF2, which controls a genetic program in the brain that promotes resistance to cognitive decline. The study was published in *Science Translational Medicine*.

The team set out to determine how environmental factors affect the brain at the neuronal level. They looked at human datasets and mouse models in parallel, and both tracks converged on MEF2 as a critical player. Cognitive resilience was highly correlated with expression of MEF2 and many of the genes that it regulates.

Researchers noted that when they knocked down MEF2 genes in the mouse brain, mice did not derive benefits from being raised in enriching conditions.

It's striking that the researchers observed the link between MEF2 and cognitive resilience in both humans and mice. Their findings suggest that enhancing the activity of MEF2 or its targets might protect against age-related dementia.

*The APOE4 gene variant – carried by just 14% of the population but nearly half of all Alzheimer's patients – is one of the most significant genetic risk factors for the disease.*

Now a study from ABI Director Li-Huei Tsai's lab shows how this gene affects brain cells' ability to metabolize lipids and respond to stress. The study in *Science Translational Medicine* shows APOE4 significantly disrupts cells' abilities to carry out their normal functions.

Treating these cells with extra choline – a safe, common nutritional supplement – could reverse many of these effects. Choline is naturally found in foods such as eggs, meat, fish, beans and nuts.

The APOE gene is known to be involved in lipid metabolism, but its role in the development of Alzheimer's hasn't been clear. To understand this connection, researchers created human induced pluripotent stem cells containing the APOE4 variant.

They then stimulated these cells to differentiate into astrocytes – the brain cells that produce the most APOE -- and treated the astrocytes with choline to promote phospholipid synthesis. They found that choline reversed much of the damage seen in those cells, including the accumulation of cholesterol and lipid droplets.

The study suggests that people with the APOE4 gene may benefit from taking choline supplements to delay or receive some protection against developing dementia or Alzheimer's disease.



Human astrocytes carrying the APOE4 variant

### Director's Letter



#### Dear Friends,

Despite continued challenges of the pandemic, we have seen reasons to hope this year. MIT's protocols keep our researchers safe while keeping up the pace of discovery. Our laboratories' work has continued, and we are happy to report progress in our research into devastating diseases of aging.

The team of Aging Brain Initiative scientists, supported by you, have melded biology and engineering in MIT style. This year led to discoveries in the genetics of neurodegeneration, possible mechanisms behind Huntington's and Parkinson's, and potential

future treatments for Alzheimer's disease. Our researchers have delved into how our brains make memories, and how the rhythms of the brain can be changed. The progress we have made is not limited to brain biology – our scientists have also made exciting advances in scientific tools, from brain imaging to financing models for drug development.

We are excited to continue our groundbreaking research with you as our partner. Thank you for your support, and Happy Holidays.

**LI-HUEI TSAI, DIRECTOR**

## Epigenomic map identifies 30,000 human disease regions

*Manolis Kellis' group in the Computer Science & Artificial Intelligence Lab have produced the most comprehensive map yet of noncoding DNA, which makes up more than 98 percent of our genome.*



The new map, called EpiMap, builds on data from several large-scale mapping consortia. "What we're delivering is really the circuitry of the human genome," Kellis says.

The study in *Nature* shows that non-coding stretches of DNA play critical roles in gene regulation and offers mechanistic insights regarding more than 30,000 noncoding variants. The researchers made their data available

to the broader scientific community and many labs are already using it.

The study demonstrates that genetic variants associated with the same trait tend to appear in tissues relevant to that trait: variants linked to intelligence are found in noncoding regions in the brain.

In addition, some traits or diseases are affected by enhancers, which are genetic sequences that help turn on genes, in many different tissue types: variants associated with coronary heart disease are active in adipose tis-

sue, coronary arteries and the liver.

Guided by these genome-wide predictions, the lab is now studying specific diseases, including profiling microglia immune brain cells from Alzheimer's patients.

Says Kellis, "We hope our predictions will be used broadly in industry and in academia to elucidate genetic variants and their mechanisms of action, focus therapies on promising targets, and accelerate drug development for many disorders."

## Computational analysis IDs new Alzheimer's risk genes

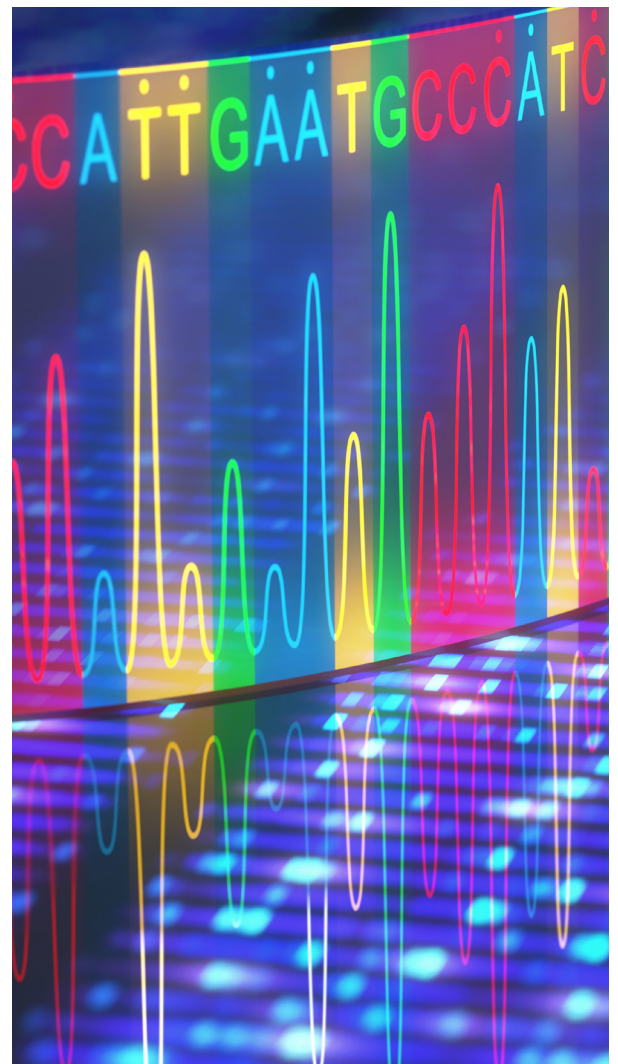
*Just how many genes are associated with the risk of Alzheimer's disease (AD) is still unclear.*

Many common, low-risk gene mutations have been identified, but because gene mutations that may incur a high risk for AD are rare in the population, they are difficult to find in traditional population genome studies. In a new paper in *Translational Psychiatry*, ABI core member Manolis Kellis, with collaborators from two large research consortia, took a new approach to find AD-associated genes.

Typical AD genome-wide association studies examine whether someone has been diagnosed with AD, and link it with their genetics. But in this work, Kellis and colleagues performed a genetic association analysis of age-of-onset of AD in a study of ~20,000 subjects, and placed more emphasis on people who do not carry the very common AD risk variant, APOE4. This age-of-onset analysis helped strengthen genetic signals, capturing both previously identified risk variants with stronger significance, and, identified two new variants in the genes ERN1 and SPPL2C.

The variant in ERN1 was very rare but presented a risk of AD of 3-4 times higher than the general population. Carriers had lower brain glucose metabolism. The SPPL2C variant was fairly common, and protective against AD, with a 30% lower likelihood of AD in people without the APOE4 allele.

The discovery of these two gene variants' association with AD will spur further investigations into the biological role of these genes and will help guide future treatments.



## Cell health systems wear down in Huntington's disease

*New analysis suggests that Huntington's disease may progress because of a degradation in cell health maintenance rather than damage from the disease itself.*



**Myriam Heiman's** lab at The Picower Institute, together with colleagues at the Sorbonne's Centre National de la Recherche

Scientifique, used an innovative computational approach to analyze vast datasets of brain cell gene expression.

They created a process called *Geomic* to integrate three large data sets which produced a clear pattern. Over time, brain cells' responses to the disease pathology — linked to toxic expansions in a gene for a protein called Huntingtin — largely continued intact, but some highly vulnerable cells lost their ability

to sustain the gene expression needed for basic systems that maintain cell health and function.

The analysis in *eLife* yielded a trove of specific gene networks governing molecular pathways that disease researchers may be able to use to sustain brain cell health amid the devastation of Huntington's disease. The new method will likely be useful for studying other neurodegenerative diseases like Alzheimer's and Parkinson's disease.

The *Geomic* source code and the data and visualizations it yielded are publicly accessible as a database.

## Researchers track brain changes in Huntington's disease

*Years before the onset of symptoms in Huntington's disease, brain imaging shows degeneration in the striatum, a brain region that controls behavior.*

As striatal neurons degenerate, their "identity" proteins, which give cells their unique functions, generally turn off. But researchers at Ann Graybiel's lab in the Department of Brain and Cognitive Sciences and the McGovern Institute have found a surprising exception: In mouse models of Huntington's disease, a cell identity protein called MOR1 becomes more abundant as striatal neurons degenerate.

They speculate that MOR1 receptors increase to compensate for plummeting levels of enkephalin, the brain's natural opioid, which is produced by the same neurons that degenerate in the earliest stages of Huntington's disease.

Because MOR1 is important for pain perception and drug-seeking, it may play a role in determining actions most

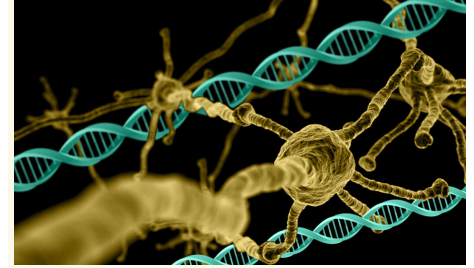


The morphine receptor, MOR1, shown in cyan in a mouse brain

likely to lead to reward.

Mood disturbances like these can predate the overt motor abnormalities of Huntington's disease by many years and can even be the most disturbing symptoms for patients and their families.

The finding that MOR1 receptors become so elevated in mood-related sites of the striatum hints at the underlying circuit dysfunction leading to these problems.



## New grants go to two Parkinson's, ALS projects

Myriam Heiman, ABI affiliate and member of The Picower Institute, has received a three-year grant from the G. Harold and Leila Y. Mathers Foundation to search for genes that could help brain cells withstand Parkinson's disease.

"There's currently no molecular explanation for the brain cell loss seen in Parkinson's disease," says Heiman. "This award will enable us to perform unbiased, genome-wide screens for genes that help brain cells survive the cellular perturbations of Parkinson's."

Additionally, Manolis Kellis, CSAIL Professor, and Myriam Heiman of The Picower Institute have won a Transformative Research Award from the National Institutes of Health to investigate the mechanisms underlying ALS and frontotemporal lobar degeneration.

The five-year project will employ innovative techniques ranging from computational, genomic and epigenomic analyses of cells to precision genetic engineering of stem cells and animal models.

## Parkinson's-linked protein affects brain energy use

In comprehensive study of a protein known to be involved in Parkinson's disease (PD), MIT scientists have found a key process affected in the PD brain. It is not yet known how the protein,  $\alpha$ -synuclein, influences disease. To address this, ABI affiliate and MIT Professor of Biological Engineering Ernest Fraenkel and collaborators measured changes in hundreds of proteins in brains of a fruit fly model of PD involving  $\alpha$ -synuclein.

Using advanced computational analysis, the team found that many changes had a common theme—how the brain uses energy. This new approach can be applied to other diseases to identify potential therapeutic pathways.

# BRAIN RHYTHMS

## Anesthesia doesn't just turn the brain 'off.' It changes its rhythms.

*Measuring neural rhythms and spikes across multiple brain areas shows how a common anesthetic induces unconsciousness, potentially improving patient safety.*

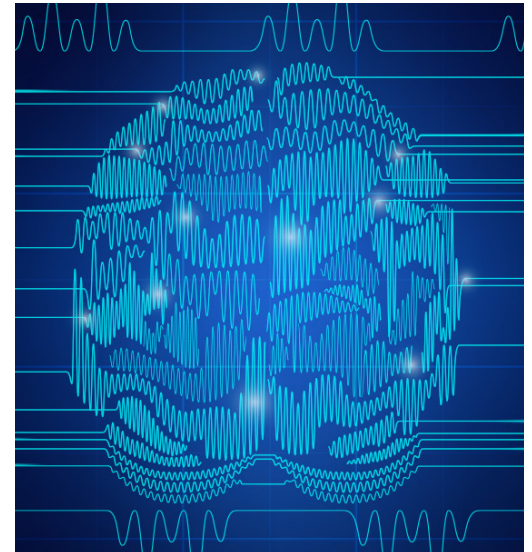
In a detailed look at how the common anesthetic propofol causes unconsciousness, a collaboration of ABI affiliate **Earl Miller's** and core member **Emery Brown's** labs shows how multiple regions in the brain are characterized by very slow rhythms of neural activity as the drug takes hold.

"There's the assumption that anesthesia simply 'turns off' the brain," said Miller. "What we show is that propofol dramatically changes the brain's rhythms."

The study in *eLife* demonstrates how anesthetic drugs change the rhythms. The main finding – a signature of very slow rhythms across the cortex – offers a model for measuring when subjects enter unconsciousness after propofol administration, how deeply they're maintained in that state, and how quickly they wake up once propofol dosing ends. The results can directly improve patient safety because these rhythms are readily visible in the operating room via EEG electrodes.

The study was conducted in animal models, allowing researchers to make detailed simultaneous measurements of activity spikes and rhythms of individual neurons in five regions of the brain, including the cortex and thalamus.

The team also showed that stimulating the thalamus with a high frequency pulse of current undid propofol's effects, restoring the synchrony of the brain's normal higher frequency rhythms and activity levels, waking the brain back up and restoring arousal.



## *Music for the mind*

*Music has a meeting with the mind both through sound perception and the concept of rhythms*



Much as music beautifully blends sound waves, many brain functions are driven by rhythmic waves of neural activity. It should be no surprise that MIT Media Lab music Professor **Tod Machover** found inspiration for his composition "Gammified" in ABI research that uses sensory stimulation to boost flagging 40Hz "gamma" rhythms in Alzheimer's disease.

In the nine-minute piece, two violins, a viola and a cello create "a musical journey" over a 40 Hz drone (akin to a piano's low E). This year after Machover made some

revisions to the 2019 composition, the Kronos Quartet released the full score free on the Web (<https://50fff.kronosquartet.org/composers/tod-machover>).

It's unknown whether listening amplifies the brain's 40Hz rhythms, but Machover says, "my hope is that the piece will promote careful listening, mental focus and emotional satisfaction, as well as invite curiosity about this exciting new world where sensory experiences – simple sounds and sights, without medicine or surgery, can target specific brain processes to cure mental diseases and to keep our minds as healthy as possible."

## Expanding tissue samples before sequencing helps pinpoint RNA



Using a novel technique for expanding tissue samples, **Ed Boyden's** lab in the Department of Biological Engineering and the McGovern Institute has devised a way to label individual molecules of messenger RNA within a sample and then sequence them.

The approach, developed with colleagues from Harvard Medical School, combines tissue expansion and *in situ* RNA sequencing, creating a new technique the researchers call expansion sequencing. The study appeared in *Science*.

Expanding the tissue before RNA sequencing offers a higher-resolution look at the RNA in cells and it makes it easier to sequence it. Once the tissue is expanded, researchers can label and sequence thousands of these molecules at a resolution that allows them to pinpoint their locations within cells and specific compartments of a cell.

The result is a unique snapshot of which genes are expressed in different parts of a cell, showing how gene expression is influenced by a cell's location or its interactions with nearby cells.

The Boyden lab has recently received a grant from the National Institute of Aging to apply this technique to mouse and human brain samples, in order to identify the neuron types in brain circuits and connections, and find whether their expression patterns change in Alzheimer's disease.

## BridgeBio Pharma's success points to a better way to finance biomedical innovation

*Bloomberg Businessweek* highlights a new way to finance biomedical innovation developed by Andrew Lo, professor of finance at MIT and affiliate of the Aging Brain Initiative.

To understand why biotech startups fail, Lo zeroed in on the "valley of death," the early period when young companies die because they can't raise money: funders like pharmaceutical companies are risk-averse, and venture capitalists are leery of the long-term investment startups need.

Lo's solution is diversification: grouping multiple startups into a single fund, allowing investors to bet on a portfolio of companies rather than one or two, then locking up financing from inception through clinical trials.

BridgeBio Pharma, Inc shows how successful this model can be. Bloomberg estimates the former startup's market value is now \$9.3 billion. Says Lo, "I'm most proud of the fact they have 20 projects of which four are in Phase 3 trials."

Lo's initial emphasis was on financing cancer therapies, but he's broadened his focus to Alzheimer's. "The more financing that comes into the industry," he says, "the faster the scientific progress we're going to make."



Paul and Priscilla Gray

## 24 Hour Challenge raises critical funds for Alzheimer's research

*Addressing the burdens of the aging brain — memory loss, cognitive decline and dementia — is a critical challenge of our time.*

MIT sponsored a micro-challenge within the School of Science's annual 24 Hour Challenge to raise funds for Aging Brain Initiative research. The micro-challenge was enormously successful: more than 300 donors gave more than \$50,000.

"This Challenge is personal for me but pervasive for all of us," said **Priscilla King Gray**, leader of the micro-challenge and wife of former MIT president **Paul Gray**, who died in 2017 after a long battle with Alzheimer's disease.

Glenda Mattes championed Gray's Challenge on behalf of her late husband, Donald Mattes, who also died of Alzheimer's. She added, "If we could change the life of one person, one family, what an achievement that would be!"

Gray says that every donation is on the path to progress. "Paul firmly believed in the power of taking action. If my story spurs someone to give — something, anything — that's one more step toward a cure."

## Microscopy innovation produces high-resolution images deep within the brain.



*Neuroscientists often use "two-photon" microscopy to make high-resolution 3D images of tissues. But two-photon scanning deep inside the brain is time-consuming and often results in blurry images.*

Now ABI-affiliate **Mriganka Sur's** lab at The Picower Institute has co-developed a new version of the technique that makes high-resolution images of deep-tissue structures as tiny as individual blood vessels and neurons in the brain — and produce the images 100 to 1,000 times faster than conventional microscopy. The research results appeared in *Science Advances*.

Imaging blood vessels in the brain is particularly useful for learning how neurodegenerative diseases like Alzheimer's affect blood flow. It could also help analyze other tissues and could even help determine the edges of a tumor.



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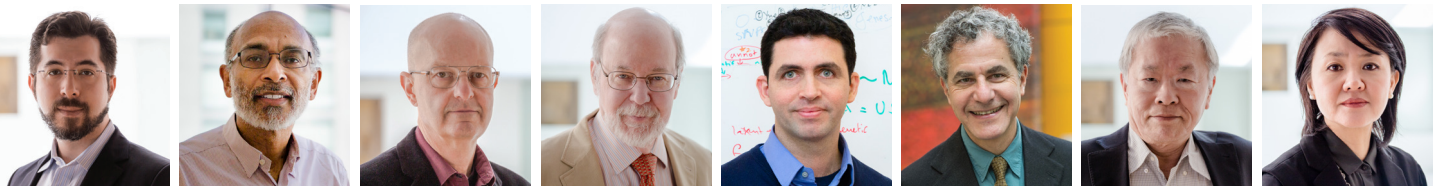
[picower.mit.edu/about/aging-brain-initiative](http://picower.mit.edu/about/aging-brain-initiative)

## 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.

## 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**, BCS, Picower; **Gloria Choi**, BCS, Picower; **Kwanghun Chung**, Chem Eng, IMES, BCS, Picower; **Joseph Coughlin**, Urban Planning, Engineering Systems; **Randall Davis**, CSAIL; **Steven Flavell**, BCS, Picower; **Ernest Fraenkel**, BioEngineering/CSAIL; **John Gabrieli**, BCS, McGovern; **Ann Graybiel**, BCS, McGovern; **Myriam Heiman**, Picower, BCS, Broad; **Rudolph Jaenisch**, Whitehead, Biology; **Alan Jasanoff**, BCS, McGovern; **J. Troy Littleton**, BCS, Picower; **Andrew Lo**, Sloan, Finance; **Tod Machover**, MIT Media Lab; **Earl Miller**, BCS, Picower; **Elly Nedivi**, BCS, Picower; **Jean-Jacques Slotine**, Mech Eng; BCS; **Mriganka Sur**, BCS, Picower; **Steven R. Tannenbaum**, Bio-engineering, Chemistry and Toxicology; **Matthew Wilson**, BCS, Biology, Picower

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

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 are proud to recognize the generosity of those friends and alumni who supported this pipeline and made our progress possible. Thank you. We deeply appreciate your trust and generous contributions. With your help, we have been able to turn curiosity into discovery, changing what we know about the world.