New Promise for Neurological Conditions

Center Launches to Study Down Syndrome

Brain Wave Stimulation May Improve Alzheimer’s Symptoms

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Neuroscience News
Gene Variants May Raise Bipolar Disorder Risk By Disrupting Protein

**A new study by Picower Institute** researchers finds that the protein CPG2 is significantly less abundant in the brains of people with bipolar disorder (BD) and shows how specific mutations in the SYNE1 gene that encodes the protein undermine its expression and its function in neurons.

The study’s mechanistic detail and specificity provide new and potentially important information for developing novel treatment strategies and for improving diagnostics, said Elly Nedivi, William R. (1964) & Linda R. Young Professor of Neuroscience and senior author of the study published in *Molecular Psychiatry*.

“It’s a rare situation where people have been able to link mutations genetically associated with increased risk of a mental health disorder to the underlying cellular dysfunction,” said Nedivi. “For bipolar disorder this might be the one and only.”

The researchers are not suggesting that the CPG2-related variations in SYNE1 are “the cause” of bipolar disorder, but rather that they likely contribute significantly to susceptibility to the disease.

Lead author Mette Rathje, a former postdoc, collected samples of postmortem human brain tissue from six brain banks. The samples included tissue from people who had been diagnosed with bipolar disorder, people who had neuropsychiatric disorders with comorbid symptoms such as depression or schizophrenia, and people who did not have any of those illnesses. Only in samples from people with bipolar disorder was CPG2 significantly lower.

Then they used deep-sequencing techniques on the same brain samples to look for genetic variations in the SYNE1 regions of BD patients with reduced CPG2 levels. They specifically looked at ones located in regions of the gene that could regulate expression of CPG2 and therefore its abundance.

Meanwhile, they also combed through genomic databases to identify genetic variants in regions of the gene that code CPG2. Those mutations could adversely affect how the protein is built and functions.

The researchers then conducted a series of experiments to test the physiological consequences of both the regulatory and protein-coding variants found in BD patients.

To test effects of non-coding variants on CPG2 expression, they cloned the CPG2 promoter regions from the human SYNE1 gene and attached them to a ‘reporter’ that would measure how effective they were in directing protein expression in cultured neurons. They then compared these to the same regions cloned from BD patients that contained specific variants individually or in combination. Some did not affect the neurons’ ability to express CPG2 but some did profoundly.

Previously Nedivi’s lab showed that human CPG2 can be used to replace rat CPG2 in culture neurons, and that it works the same way to regulate glutamate receptor levels. Using this assay they tested which of the coding variants might cause problems with CPG2’s cellular function. They found specific culprits that either reduced the ability of CPG2 to locate in the “spines” that house excitatory synapses or that decreased the proper cycling of glutamate receptors within synapses.

**ON THE COVER**

*TOP:* Microglia (stained green) gang up on an amyloid beta plaque in the cortex of a mouse. *BOTTOM:* Neural progenitor cells used in Down syndrome research.
How Cues From Prior Context Heighten Recall

We often find that when we return to a context where an episode first happened, specific and vivid memories can come flooding back. In a new study in *Neuron*, Picower Institute scientists report the discovery of a mechanism the brain may be employing to make that phenomenon occur.

“Suppose you are driving home in the evening and encounter a beautiful orange twilight in the sky, which reminds you of the great vacation you had a few summers ago at a Caribbean island,” said study senior author Susumu Tonegawa, Picower Professor of Neuroscience at MIT. “This initial recall could be a general recall of the vacation. But moments later, you may get reminded of details of some specific events or situations that took place during the vacation which you had not been thinking about.”

At the heart of that second stage of recall, where specific details are suddenly vividly available, is a change in the electrical excitability of “engram cells,” or the ensemble of neurons that together encode a memory through the specific pattern of their connection. In the new study, Tonegawa’s lab, led by postdoc Michele Pignatelli and former member Tomás Ryan showed that after mice formed a memory in a context, the engram cells encoding that memory in a brain region called the hippocampus would temporarily become much more electrically excitable if the mice were placed back in the same context again. So for instance, if they were given a little shock in a specific context one day, then the engram cells would be much more excitable for about an hour after they were put back in that same context the next day.

The specific change in the engram cells’ electrical properties has some direct implications for learning and behavior that hadn’t been appreciated before. Importantly, during that hour after returning to the initial context, because of the engrams’ elevated excitability, mice proved better able to learn from a shock in that context and better able to distinguish between that and distinct contexts even if they shared some similar cues.

Experiments showed that reduced expression of potassium inward rectifier ion channels causes the excitability increase and protein synthesis ends it after about an hour.

Mapping the Brain with ‘SHIELD’

Kwanghun Chung’s research group has devised a new way to preserve biological tissue, allowing them to visualize proteins, DNA, and other molecules within cells, and to map the connections between neurons.

The researchers showed that they could use this method, known as SHIELD, to trace the connections between neurons in a part of the brain that helps control movement and other neurons throughout the brain.

Brain tissue is very delicate and cannot be easily studied unless steps are taken to preserve the tissue from damage. Chung and his colleagues hypothesized that they might be able to preserve tissue using molecules called polyepoxides — reactive organic molecules that are often used to produce glues. They tested several commercially available polyepoxides and discovered one that had distinctive structural traits that made it ideally suited for their purposes.

The epoxide they chose has a flexible backbone and five branches, each of which can bind to certain amino acids (the building blocks of proteins), as well as other molecules such as DNA and RNA. The flexible backbone allows the epoxides to bind to several spots along the target molecules, and to form cross-links with nearby biomolecules. This renders individual biomolecules and the entire tissue structure very stable and resistant to damage from heat, acid, or other harmful agents. SHIELD also protects key properties of biomolecules, such as protein fluorescence and antigenicity.

Chung is now leading a team of researchers from several institutions that recently received a National Institutes of Health grant to use this technique to produce three-dimensional maps of the entire human brain. “We will be working with Matthew Frosch’s group at MGH, Van Wedeen’s group at MGH, Sebastian Seung’s group at Princeton, and Laura Brattain’s group at MIT Lincoln Lab to generate the most comprehensive brain map yet,” he says.

The researchers showed that they could use this method, known as SHIELD, to trace the connections between neurons in a part of the brain that helps control movement and other neurons throughout the brain.
The Circuits That May Help You Keep Your Cool

People often need to moderate their level of arousal so that they can be alert without being overly excited. A new study by neuroscientists at MIT’s Picower Institute might help to explain how the brain strikes that balance.

“Human beings perform optimally at an intermediate level of alertness and arousal where they are attending to appropriate stimuli rather than being either anxious or somnolent,” said Mriganka Sur, Paul and Lilah E. Newton Professor in the Department of Brain and Cognitive Sciences. “But how does this come about?”

Postdoc Vincent Breton-Provencher brought this question to the lab and led the study published January 14 in Nature Neuroscience. In a series of experiments in mice, he shows how connections from around the mammalian brain stimulate two key cell types in a region called the locus coeruleus (LC) to moderate arousal in two different ways. A region particularly involved in exerting one means of this calming influence, the prefrontal cortex, is a center of executive function, which suggests there may indeed be a circuit for the brain to attempt conscious control of arousal.

By explaining more about how the brain keeps arousal in check, Sur said, the study therefore might also provide insight into the neural mechanisms contributing to anxiety or chronic stress, in which arousal appears insufficiently controlled. It might also provide greater mechanistic understanding of why cognitive behavioral therapy can help patients manage anxiety, Sur added.

Crucial characters in the story are neurons that release the neurotransmitter GABA, which has an inhibitory effect on the activity of receiving neurons. Breton-Provencher observed that LC-GABA neurons were located within the LC close to neurons that release noradrenaline (NA), which stimulates arousal. He was also able to show that the LC-GABA and LC-NA neurons connect.

In his experiments Breton-Provencher was able to see that the LC is actually home to two different kinds of inhibitory control. One type came about from those inputs — for instance from sensory processing circuits — that simultaneously connected into LC-GABA and LC-NA neurons and reduced arousal arising from individual startling stimuli. The other type came about from inputs — notably including from the prefrontal cortex — that only connected into LC-GABA, but not LC-NA neurons. In that case, LC-GABA activity correlated with an overall reduced amount of arousal, independent of how startling an individual stimulus was.

Scope Advance Allows Deepest Ever Look Into Awake Brain

With a substantial refinement of three-photon microscope technology, MIT scientists have conducted the first-ever study of stimulated neural activity in an awake mouse through every visual cortex layer and notably the mysterious “subplate” below.

In the study, published in Nature Communications, the team showed that as mice watched visual stimuli, their human observers could measure patterns of activity among neurons in all six layers of visual cortex and the subplate, providing new data about their role in how mammals process vision. Moreover, through a series of careful experiments, the researchers were able to show that the light they sent in, as well as the light that came back out, neither damaged, nor even altered, the cells they measured.

“By optimizing the optical design and other features for parameters for making measurements in the live brain, we were able to actually make novel discoveries that were not possible before,” said co-corresponding author Mriganka Sur, Newton Professor of Neuroscience in the Picower Institute. The paper’s co-lead authors are postdocs Murat Yildirim and Hiroki Sugihara. The other corresponding author is Peter So, professor of mechanical engineering and biological engineering.

Sur and So’s labs at MIT have joined in pushing the frontiers of multiphoton microscopy. In the new study they show they’ve now taken it far enough to study live neural activity. To do that, the team sought to refine many different parameters of both the laser light and the scope optics, based on meticulous measurements of properties of the brain tissue they were imaging. For instance, they not only measured the energy at which cells started to show overt damage (about 10 nanojoules), but also measured the power at which cells would start to behave differently, thereby producing data influenced by the measurement (2 to 5 nanojoules). With precision and purpose to deliver lower energy levels, the scientists optimized the scope to emit incredibly short pulses of light lasting for a “pulse width” of only 40 femtoseconds, or quadrillionths of a second, and painstakingly arranged the optics to maximize the collection of the light that molecules, excited by the incoming laser energy, would emit back.


An Unusual Hallmark of Neuron Aging

As we age, neurons in our brains can become damaged by free radicals. MIT biologists including Picower Institute faculty member Myriam Heiman have now discovered that this type of damage, known as oxidative stress, produces an unusual pileup of short snippets of RNA in some neurons.

This RNA buildup, which the researchers believe may be a marker of neurodegenerative diseases, can reduce protein production. The researchers observed this phenomenon in both mouse and human brains, especially in a part of the brain called the striatum — a site involved in diseases such as Parkinson’s and Huntington’s.

The researchers found that a type of nerve cell in the striatum — D1 neurons from aged mice (but not neurons in younger mice or D2 neurons from aged mice), and to explore how they were affected by age. To their surprise, a mysterious result emerged — in their 70s or 80s.

In separate groups of mice, the researchers tagged ribosomes from either D1 or D2 spiny projection neurons, which make up 95 percent of the neurons found in the striatum. They labeled these cells in younger mice (6 weeks old) and 2-year-old mice, which are roughly equivalent to humans in their 70s or 80s.

The researchers had planned to look for gene expression differences between those two cell types, and to explore how they were affected by age. To their surprise, a mysterious result emerged — in D1 neurons from aged mice (but not neurons from young mice or D2 neurons from aged mice), they found hundreds of genes that expressed only a short fragment of the original mRNA sequence. These snippets, known as 3’ untranslated regions (UTRs), were stuck to ribosomes, preventing the ribosomes from assembling normal proteins.

The researchers believe this RNA buildup, which the researchers believe may be a marker of neurodegenerative diseases, can reduce protein production. The researchers observed this phenomenon in both mouse and human brains, especially in a part of the brain called the striatum — a site involved in diseases such as Parkinson’s and Huntington’s.


Gut-Brain Connection Guides Worm Feeding Behavior

When a hungry worm encounters a rich food source, it immediately slows down so it can devour the feast. Once the worm is full, or the food runs out, it will begin roaming again. A new study from the Picower Institute lab of Steven Flavell reveals key new details about how the worm’s digestive tract signals the brain when to linger in a plentiful spot.

The researchers found that a type of nerve cell found in the gut of the worm Caenorhabditis elegans is specialized to detect when bacteria are ingested; once that occurs, the neurons release a neurotransmitter that signals the brain to halt locomotion. The researchers also identified new ion channels that operate in this specialized nerve cell to detect bacteria.

The digestive tract has its own semi-independent nervous system, known as the enteric nervous system. While the full complexities of the human enteric nervous system have yet to be fully understood, many researchers use C. elegans, which has a much simpler nervous system, as a model to study feeding behavior. Researchers have previously shown that food greatly influences the locomotion of C. elegans.

“There was behavioral evidence that C. elegans nervous system is receiving information about the food in the environment, but we didn’t know how that worked,” said Flavell, Lister Brothers Career Development Assistant Professor of brain and cognitive sciences. Flavell is the senior author of the study in Cell. Jeffrey Rhoades, a former technical assistant, is the paper’s first author.


System Provides Real-Time Readout of Where Rats Think They Are

The rat in a maze may be one of the most classic research motifs in brain science, but a new innovation described in Cell Reports by an international collaboration of scientists shows just how far such experiments are still pushing the cutting edge of technology and neuroscience alike.

In the study, the team including Matthew Wilson, Sherman Fairchild Professor of Neuroscience in the Picower Institute, demonstrates technology that allowed them to read out neural signals in real-time as a rat runs a maze, with a high degree of accuracy and the ability to account for the statistical relevance of the readings almost instantly after they are made.

The ability to so robustly track the rat’s spatial representations in real-time opens the door to a whole new class of experiments, the researchers said. They predict these experiments will produce new insights into learning, memory, navigation and cognition by allowing them to not only decode rat thinking as it happens, but also to instantaneously intervene and study the effects of those perturbations.

“The use of real-time decoding and closed-loop control of neural activity will fundamentally transform our studies of the brain,” Wilson said.

Wilson and former postdocs Zhe (Sage) Chen and Fabian Kloosterman collaborated on the paper in which they boosted the speed of their system’s open-source software by running in on a GPU chip. It performed 20-50 times faster than using conventional CPUs.

As part of MIT’s launch of the Schwarzman College of Computing in March, the School of Humanities Arts and Social Sciences asked thought leaders to contribute essays on Ethics, Computing and Artificial Intelligence. Matthew Wilson, Sherman Fairchild Professor of Neuroscience, wrote the following in response to the question: “How might insights and research from neuroscience accelerate the development of ethical safeguards for computing and AI tools?”

The effort to develop machines that can operate on an intellectual par with humans — what is called artificial general intelligence (AGI) — naturally draws parallels to biological intelligence as the capability being mimicked. The question is, should we hold artificial intelligence (AI) systems to the same standards as the average human? Will we expect AIs to perform at the level of an ideal human? Or will we expect them to exceed humans in ways both expected and unexpected?

Our current sense of the impact AIs will have on society has emerged from advances in specific applied domains: They drive our cars; they diagnose our medical conditions; and they understand our language. In each of these instances, AIs are given specific tasks with clear metrics of performance. But as the complexity of the problem domains increases, the difficulty of implementing AIs that can solve general problems in transparent and predictable ways increases. Understanding how they are solving problems will be as important as measuring how well they are solving problems.

In human society, one way to address such questions is to apply ethics — the established norms of behavior that create an environment of trust among people. We trust that individuals will perform actions that are both constrained and motivated in clearly understood ways. Much of this trust in human intelligence is derived from our common understanding of the innate capacities of other humans.

We share a foundation in how we perceive the world, how we experience and remember our interactions with the world, how we evaluate risks and plan for the future, and how we learn from our actions and the actions of others. Each of these serves to define both our common understanding of what it means to be human and our unique individuality.

**Innate morality in humans**

One key element of our humanity is the assumption of innate morality — that we can predict moral judgments in novel situations. Work being done at MIT has shown the youngest children have an understanding of moral behavior that can serve as a foundation for predicting future behavior. Often this capacity is framed in terms of how we resolve moral dilemmas, but the issue is not determining the right choice, but rather how the choice will be made. Understanding how this kind of innate morality arises in human intelligence may be an important step in incorporating such a capacity into artificial intelligences.

Having developed an AGI, one objective might be to determine how “human” it was. Some might challenge this goal, arguing that there is no reason an AI should be constrained to perform like a biological intelligence. And, it’s true that we might not need an AI driving a car to behave like a human driver; in fact, we might argue that a primary motivation for developing such an AI is that it NOT drive like a human. In such cases, our trust in an AI could be derived from our ability to predict their behavior in all relevant situational contexts.

However, an AGI by definition will not be able to rely on comprehensive situational contextual knowledge and yet will have to have generalizable behavior that still conforms to the norms of conduct that we would expect of an ideal human. What are those human norms? How would we incorporate them into the programming of an AGI? How would we assess the competence of such an AGI to respond appropriately in novel situations?

**Developing artificial emotional intelligence**

Emotions can be thought of as representing the kind of generalizable situational context that could be used to drive predictable behavior under conditions of novelty. Developing such artificial emotional intelligence — and evaluating it against human emotional intelligence — are active areas of research that might prove crucial in creating trustworthy AGIs.

An interesting extension to this is the question of how artificial agents that are imbued with human-like emotional intelligence would blur the line between man and machine. This has been a popular premise in science fiction, but considering how we will deal with this development as it becomes science fact will become part of a broader conversation on society, technology, and human rights.

Of course, there are many other important considerations in developing AI, such as issues of job displacement and wealth distribution, all of which point to the inextricable relationship between technology and society, artificial intelligence and biological intelligence. This relationship will form the basis of ongoing research and development in these rapidly expanding fields.
New Faculty Member Studies the IMMUNE System Effect on the BRAIN

Gloria Choi, the newest faculty member of the Picower Institute, studies the surprising ways that the immune system influences the brain. She’s revealed the mechanism, for example, by which maternal infection during pregnancy can lead to a neurodevelopmental disorder in offspring. But she might have pursued an entirely different career if her mother hadn’t talked her out of it without saying a word.

On the phone one day during her first year at UC Berkeley, Choi asked her mom what she’d think about her studying accounting. “There was no answer on the other side,” recalled Choi, now the Samuel A. Goldblith Career Development Assistant Professor of Applied Biology. “So I said, ‘Ok, maybe not’.”

Choi initially gravitated to science and math because her family had immigrated to Southern California from South Korea when she was a teenager and the language barrier was less of a problem in those classes. Throughout high school and college she found she had a knack for biology, so she continued on to graduate school at Caltech. There she found a mentor in Professor David Anderson, a prominent biologist who was beginning to take an intensive interest in brain. She became one of the first students in his lab to tackle research in the central nervous system.

Her thesis research, published in Neuron in 2005, identified a molecular pathway the brain employs in circuits between the amygdala and hypothalamus to mediate between conflicting primal behaviors such as mating and defending oneself from predators.

A Leap of Faith Across the Country

At Caltech, she could go home every week to see her parents and grandmother (and to bring her laundry). Taking her next step, she said, was therefore very difficult: moving from Pasadena to a post-doctoral fellowship at Columbia University. But it was no ordinary opportunity to work in the lab of Professor Richard Axel, who in 2004 shared the Nobel Prize with Linda Buck for key discoveries of the structure of the olfactory system.

Axel urged Choi to model the big picture of what she was trying to study — to hypothesize not just one step of a process but to formulate a potential explanation of a whole phenomenon. In Axel’s lab she studied the processes that link the input of a smell to the output of a behavior through learning.

When she joined the MIT Brain and Cognitive Sciences faculty in 2013, she did so in part because she felt the environment would push her to blaze her own trail.

“I’m not an adventurous person,” Choi said. “I felt like this could be a place where I will be naturally pushed to test my limits because this is a place of innovation.”

A Blossoming Field Yields Autism Insights

The new trail led to “neuroimmunology.” Her lab studies the interaction of the immune system with the brain and the effects of that interaction on neurodevelopment, behavior and mood. She is particularly interested in how cytokines, proteins that immune cells use to communicate, may act as neuromodulators that influence the development and activity of neurons in the cortex.

In the same spirit she learned in Axel’s lab, she has embarked on a collaboration that has richly modeled the process by which maternal infection can lead to aberrant neurodevelopment. In this research, she works side-by-side with her husband Jun Huh, an immunologist across the Charles at Harvard Medical School.

In a 2016 paper in Science, their team showed in a mouse model of maternal immune activation (MIA) that the link between MIA and the development of autism-like behavioral abnormalities in offspring was a particular type of maternal immune system T-cell and its secretion of the cytokine IL-17a, which reaches the brain of the fetus. The collaboration followed with two papers in Nature in September 2017. One showed the phenomenon required the presence of maternal intestinal bacteria that promote the differentiation of the T cell. The other showed that excessive IL-17a in the brain during development leads to a deficit of neural inhibition specifically in the S1DZ region of the cortex. The team showed that by intervening to reduce excess activity there, they could mitigate behavioral abnormalities associated with maternal infection.

Motivated by those findings, Choi’s long-term translational goal is to develop ways to assess the risk of maternal infection leading to neurodevelopmental disorders, prevent the development of disease, and mitigate it post-development. Also, because her research has identified the S1DZ region, which is hypothesized to be important for proprioception, or the brain’s sense of where the body is in space, she is also studying the connection between that and social behavior.

“As we gather more data about the interaction of these two systems, we realize it’s such an important interaction to look at,” she said. “It’s not just us. The field of neuroimmunology is blossoming.”

So is Choi’s career choice of science.
Tsai Earns Hans Wigzell Research Foundation Science Prize

The Hans Wigzell Research Foundation named neuroscientist Li-Huei Tsai, Picower Professor and director of The Picower Institute for Learning and Memory at MIT, the winner of The Hans Wigzell Research Foundation Science Prize for 2018. To receive the prize and deliver a talk about her work, Tsai traveled to Stockholm Feb. 14.

“The prize is given to professor Li-Huei Tsai for her innovative research in trying to understand the etiology and possible treatment of Alzheimer’s disease,” the Foundation stated in the announcement of the $100,000 prize. “Professor Tsai has in her research made a series of impressive findings with regard to this disease.”

In decades of research with collaborators, postdocs and students, Tsai has led several fundamental and translatable discoveries about biological mechanisms underlying neurodegeneration including specific aberrations in epigenetic gene regulation, enzyme pathways and repair of DNA damage. Tsai and collaborators have also uncovered substantial evidence that impaired neuronal synchrony may underlie Alzheimer’s progression, an insight that has allowed her to demonstrate a non-invasive treatment approach using light and sound stimuli to drive neural oscillations, engage the brain’s immune system, reduce pathology, and improve functionality in multiple mouse models (see page 10). Testing of the technique has recently begun in humans.

“This treatment has resulted in dramatic improvements of the diseased animals both with regard to pathology and performance,” the foundation noted. “Her research has rapidly resulted in the start of advanced, clinical trials in Alzheimer’s patients.”

Tsai, who also directs the Aging Brain Initiative at MIT, said she was honored to earn the Wigzell Foundation’s recognition. Hans Wigzell is a former President of the Karolinska Institute and Chairman of the Nobel Prize Committee of the Institute.

“I am deeply grateful to Professor Wigzell and the Foundation for this award,” Tsai said. “The prize provides my team with great inspiration and resources to continue our work to understand the biology of neurodegeneration and to translate our findings to effective treatments for Alzheimer’s and other diseases.”

Brown wins 2018 Dickson Prize in Science

Carnegie Mellon University recently announced that Emery N. Brown, a member of the Picower Institute and the Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience at MIT, has won the 2018 Dickson Prize in Science.

“Dr. Brown is one of the world’s leading physician-scientists,” the University stated in its announcement. “Dr. Brown’s outstanding achievements have earned him the distinction of being one of only 21 people elected to all three branches of the National Academies of Science. He is considered the ‘world’s expert on statistical analysis of neuronal data’, according to CMU faculty nominator Robert E. Kass, ‘and his research on anesthesia has been ‘truly transformative’ to that field.’

Brown directs an interdisciplinary team comprised of anesthesiologists, neuroscientists, bioengineers, mathematicians, neurologists and a neurosurgeon from MGH, MIT and Boston University that is studying the neuroscience of general anesthesia, CMU’s announcement noted. Brown also directs the Neuroscience Statistics Research Laboratory at MGH and MIT where members develop statistical methods and signal processing algorithms to analyze data collected in neuroscience experiments.

Carnegie Mellon’s Dickson Prize in Science is awarded annually to the person who has been judged by the university to have made the most progress in the scientific field in the United States for the year in question. At Carnegie Mellon, the field of science is interpreted to include the natural sciences, engineering, computer science or mathematics. The first Dickson Prize in Science was awarded in 1970.

In accepting the award, Brown credited the many people he has worked with at MIT, MGH, BU, and Harvard.

“I am extremely honored to receive the 2018 Dickson Prize in Science and to join the esteemed ranks of its past recipients,” he said. “I am especially grateful to all of the many students, post-docs and colleagues whose successful collaborations have led to this recognition.”

Brown was due to deliver a lecture upon receiving the award in January but the event had to be postponed because of the extreme cold brought by a polar vortex. It will be rescheduled soon.
‘CAREER’ Award Funds Flavell Study of Behavioral States

Picower Institute faculty member Steven Flavell wants to know why if neurons fire on a timeframe of mere milliseconds, behaviors like sleep or emotions like sadness can last for hours or days. A new CAREER Award from the National Science Foundation will help him find out.

“One of the most remarkable things about the brain is that it can generate behaviors that unfold over a wide range of different timescales,” said Flavell, Lister Brothers Career Development Assistant Professor in the Department of Brain and Cognitive Sciences at MIT.

To tackle such a big, complex and universal question about animal behavior, Flavell is working with a small-scale model organism: the tiny roundworm C. elegans.

“C. elegans is an attractive system for these studies because its nervous system consists of just 302 neurons,” he said. “A full understanding of how neural circuits give rise to behavior requires detailed knowledge across many scales of analysis: from molecular events in single neurons to large-scale patterns of neural activity to emergent animal behaviors.”

Using newly developed imaging tools and other cutting-edge methods, Flavell’s lab will be able to observe mechanisms and activity at all of these scales and experimentally manipulate them, producing the big and small picture of how the worm’s nervous system produces and sustains states like sleep and wakefulness. Those findings can then inform studies of more complex animals where these questions are currently much more difficult to study.

The five-year, $762,000 award began April 1. The CAREER award is the NSF’s most prestigious award given out annually to early-stage faculty.

Nedivi Named Inaugural Young Professor

Elly Nedivi, a professor in the Picower Institute and the Departments of Brain and Cognitive Sciences and Biology, has been named the inaugural William R. (1964) & Linda R. Young Professor of Neuroscience, the MIT School of Science announced.

Nedivi, an MIT faculty member since 1998, studies the cellular mechanisms that underlie activity-dependent plasticity in the developing and adult brain through studies of neuronal structural dynamics, identification of the participating genes, and characterization of the proteins they encode.

Her work to identify “candidate plasticity genes” has yielded many insights, including elucidating the neuronal and synaptic functions of two previously unknown CPGs: CPG2 and CPG15. In a study published earlier this year (see page 2), her lab showed that the protein CPG2 is significantly less abundant in the brains of people with bipolar disorder and showed how specific mutations in the SYNE1 gene that encodes CPG2 undermine the protein’s expression and its function in neurons, potentially contributing to disease.

Motivated by the large number of CPGs that affect neuronal structure, her lab has also been collaborating with that of Peter So in MIT’s Department of Mechanical Engineering to develop multi-color two photon microscopy for large volume, high resolution imaging of dendritic arbor and synaptic structural dynamics in vivo. Nedivi’s lab was the first to show unambiguous evidence of dendritic arbor remodeling in the adult brain, and identify inhibitory connections as the most plastic component of experience-dependent circuit rearrangements.

Nedivi thanked the Youngs for their support of neuroscience research at MIT.

“I recently met the Youngs, and share their view that study of the brain and mind is an area of science with tremendous potential to improve people’s lives,” she said. “I respect their wish to give back to MIT, and am deeply honored to be named the inaugural William R. (1964) & Linda R. Young Professor of Neuroscience.”
By exposing mice to a unique combination of light and sound, neuroscientists in the Picower Institute for Learning and Memory have shown that they can improve cognitive and memory impairments similar to those seen in Alzheimer’s patients. This noninvasive treatment, which works by inducing brain waves known as gamma oscillations, also greatly reduced the number of amyloid plaques found in the brains of these mice. Plaques were cleared in large swaths of the brain, including areas critical for cognitive functions such as learning and memory.

“When we combine visual and auditory stimulation for a week, we see the engagement of the prefrontal cortex and a very dramatic reduction of amyloid,” said study author Li-Huei Tsai, Picower Professor of Neuroscience and director of the Picower Institute and MIT’s Aging Brain Initiative. Further study will be needed, Tsai said, to determine if this type of treatment will work in human patients. Her lab has already performed some preliminary safety tests of this type of stimulation in healthy human subjects.

Former Tsai lab graduate student Anthony Martorell, who defended his dissertation on the research Feb. 28, and Georgia Tech graduate student Abigail Paulson are the lead authors of the study, which appeared March 14 in Cell.

**Brain Wave Stimulation May Improve Alzheimer’s Symptoms**

The brain’s neurons generate electrical signals that synchronize to form brain waves in several different frequency ranges. Previous studies have suggested that Alzheimer’s patients have impairments of their gamma-frequency oscillations, which range from 25 to 80 hertz (cycles per second) and are believed to contribute to brain functions such as attention, perception, and memory.

In 2016, Tsai and her colleagues first reported the beneficial effects of restoring gamma oscillations in the brains of mice that are genetically predisposed to develop Alzheimer’s symptoms. In that study, the researchers used light flickering at 40 hertz, delivered for one hour a day. They found that this treatment reduced levels of beta

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**Image:**

Imaging of a clarified mouse brain, stained to highlight amyloid, shows much more of the protein in the untreated brain on the left vs the treated brain on the right.
amyloid plaques and another Alzheimer’s-related pathogenic marker, phosphorylated tau protein. The treatment also stimulated the activity of debris-clearing immune cells known as microglia.

In that study, the improvements generated by flickering light were limited to the visual cortex. In their new study, the researchers set out to explore whether they could reach other brain regions, such as those needed for learning and memory, using sound stimuli. They found that exposure to one hour of 40-hertz tones per day, for seven days, dramatically reduced the amount of beta amyloid in the auditory cortex (which processes sound) as well as the hippocampus, a key memory site that is located near the auditory cortex.

“What we have demonstrated here is that we can use a totally different sensory modality to induce gamma oscillations in the brain. And secondly, this auditory-stimulation-induced gamma can reduce amyloid and Tau pathology in not just the sensory cortex but also in the hippocampus,” Tsai said.

The researchers also tested the effect of auditory stimulation on the mice’s cognitive abilities. They found that after one week of treatment, the mice performed much better when navigating a maze requiring them to remember key landmarks. They were also better able to recognize objects they had previously encountered. They also found that auditory treatment induced changes in not only microglia, but also the blood vessels, possibly facilitating the clearance of amyloid.

**Dramatic effect**

The researchers then decided to try combining the visual and auditory stimulation, and to their surprise, they found that this dual treatment had an even greater effect than either one alone. Amyloid plaques were reduced throughout a much greater portion of the brain, including the prefrontal cortex, where higher cognitive functions take place. The microglia response was also much stronger. “These microglia just pile on top of one another around the plaques,” Tsai said. “It’s very dramatic.”

The researchers found that if they treated the mice for one week, then waited another week to perform the tests, many of the positive effects had faded, suggesting that the treatment would need to be given continually to maintain the benefits.

In an ongoing study, the researchers are now analyzing how gamma oscillations affect specific brain cell types, in hopes of discovering the molecular mechanisms behind the phenomena they have observed. Tsai said she also hopes to explore why the specific frequency they use, 40 hertz, has such a profound impact.

The combined visual and auditory treatment has already been tested in healthy human volunteers, to assess its safety, and the researchers are now beginning to enroll patients with early-stage Alzheimer’s to study its possible effects on the disease.

“Though there are important differences among species, there is reason to be optimistic that these methods can provide useful interventions for humans,” said Nancy Kopell, a professor of mathematics and statistics at Boston University, who was not involved in the research. “This paper and related studies have the potential for huge clinical impact in Alzheimer’s disease and others involving brain inflammation.”

The research was funded, in part, by the Robert and Renee Belfer Family Foundation, the Halis Family Foundation, the JPB Foundation, and the National Institutes of Health.

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When we combine visual and auditory stimulation for a week, we see the engagement of the prefrontal cortex and a very dramatic reduction of amyloid.

*Li-Huei Tsai*
On March 20, the day before World Down Syndrome Day, MIT launched the Alana Down Syndrome Center, an innovative new research endeavor, technology development initiative, and fellowship program with a $28.6 million gift from Alana Foundation, a nonprofit organization started by Ana Lúcia Villela of São Paulo, Brazil.

Hosted out of the Picower Institute, the center will engage multidisciplinary research across neuroscience, biology, engineering, and computer science labs to understand the biology and neuroscience of the disorder. The gift will also fund a four-year program with MIT’s Deshpande Center for Technological Innovation called “Technology to Improve Ability,” in which creative minds around MIT will be encouraged and supported in designing and developing technologies that can improve life for people with different intellectual abilities or other challenges.

Together, the center and technology program will work to accelerate the generation, development, and clinical testing of novel interventions and technologies to improve the quality of life for people with Down syndrome (DS). Moreover, the postdoctoral and graduate fellowships will increase the number of scientists trained in DS research for generations to come.

“At MIT, we value frontier research, particularly when it is aimed at making a better world,” says MIT President L. Rafael Reif.

“The Alana Foundation’s inspiring gift will position MIT’s researchers to investigate new pathways to enhance and extend the lives of those with Down syndrome. We are grateful to the Foundation’s leadership—President Ana Lúcia Villela and Co-President Marcos Nisti—for entrusting our community with this critical challenge.”

Villela and Nisti have two daughters, one with DS. In 2015 they gave MIT $1.7 million to fund studies in the lab of Picower Institute director Li-Huei Tsai to create new laboratory models of the condition and to improve understanding of the mechanisms of the disorder and potential therapies. With that support, Hiruy Meharena, senior fellow in Tsai’s neuroscience lab, has already been deeply engaged in studying DS’s impact in the brain at the cellular and genomic level.

$28.6 MILLION GIFT

from Alana Foundation will fund science, innovation, education to advance understanding, ability, inclusion.
In creating the new center, MIT and Alana Foundation officials said they are building on that partnership to promote discovery and technology development aimed at helping people with different abilities gain greater social and practical skills to enhance their participation in the educational system, in the workforce, and in community life. “We couldn’t be happier and more hopeful as to the size of the impact this center can generate,” Villela said. “It’s an innovative approach that doesn’t focus on the disability but, instead, focuses on the barriers that can prevent people with Down syndrome from thriving in life in their own way.”

Nisti added, “This gift represents all the trust we have in MIT especially because the values our family hold are so aligned with MIT’s own values and its mission.”

**A Robust Research Agenda**

DS, also known as trisomy 21, is characterized by extra genetic material from some or all of chromosome 21 in many or all of an individual’s cells and occurs in one out of every 700 babies in the United States. Though the chromosomal hallmark of DS has been well known for decades, and advances in research, health care and social services have doubled lifespans over the past 25 years, significant challenges remain for individuals with different abilities and their families because the underlying neurobiology of the disorder is complex.

The center will be co-directed by Tsai, the Picower Professor of Neuroscience, and Angelika Amon, the Kathleen and Curtis Marble Professor in Cancer Research. They will collaborate closely with Ed Boyden, the Y. Eva Tan Professor in Neurotechnology and computer science Professor Manolis Kellis, director of MIT’s Computational Biology Group.

The new center will employ cutting-edge techniques to study the neurosciences of DS with two main focuses: systems and circuits as well as genes and cells. At the March 20 launch event that packed Building 46’s Singleton Auditorium, the scientists laid out their research plans for an audience including leaders of global and local DS organizations.

Tsai’s lab focuses on neurodegenerative disorders, such as Alzheimer’s disease (AD), which shares important underlying similarities with DS. That’s because the amyloid precursor protein gene APP, is found on chromosome 21. As a result of having an extra copy, people with Down syndrome typically share some of the underlying amyloid protein pathology of people with AD and are at a much higher risk of developing AD as they age.

In the new center, Tsai said, she is eager to learn whether an innovative, non-invasive potential AD treatment her lab has developed could help people with DS. Called GENUS for “Gamma ENtrainment Using Sensory stimuli” the method uses lights that flicker and sound that buzzes at the frequency of 40 Hz to stimulate 40 Hz gamma rhythms in the brain. In experiments with mice (see page 10), the technique reduces AD pathology and improves learning and memory, in part by activating the brain’s immune cells, microglia, to clear out harmful amyloid and tau proteins.

Boyden, who has collaborated with Tsai in developing GENUS, said he will bring two other novel technologies from his lab to the center’s work. A technique called “**Temporal Interference,”** which he developed with collaborators from MIT’s Computational Biology Group.

Kellis’s work uses advanced computational approaches to help explain the complex question of how genomic differences lead to differences in health and cognitive functions.

In all the collaborations in the center are aimed at generating understanding and technology to help people with DS live healthier lives with fuller participation in society. For the purpose, Reif said in his remarks, the center brings together “a world class team, on a world class mission.”
In their collaboration to help elucidate and mitigate Alzheimer’s disease and other neurological conditions, the labs of neuroscientist Li-Huei Tsai and computer scientist Manolis Kellis are two sides of the same coin on two sides of Vassar Street.

Bringing complementary skills to a shared mission as part of MIT’s Aging Brain Initiative, the team seamlessly blends and advances some of the hottest and most powerful methods in science — statistical genetics, computational genomics, epigenomics, machine learning, single-cell profiling, “big data” integration, induced stem-cell reprogramming, mini-brain organoids, tissue engineering, and Crispr/Cas9 genetic manipulation.

This allows their teams to study genetic and molecular differences between healthy and diseased samples from multiple brain regions of human and mouse, integrate and analyze the resulting data to identify significant disease-driver genes and the cell types where they act, and engineer cells, tissues and mouse models to test their hypotheses and discover therapeutic interventions.

“Working together, we have the opportunity to garner big data from a large number of human subjects to elucidate the driver genes and pathways that are novel but key to the disease,” said Tsai, Picower Professor and director of the Picower Institute for Learning and Memory. “We can then test these genes/pathways in the induced pluripotent stem cells (iPSC) system coupled with Crispr/Cas9 to manipulate the genome. We can induce the iPS cells into all major brain cell types, and dissect the contributions of each of these cell types to disease.”

It’s a joint research venture that’s as close, cutting-edge, and multidisciplinary as any at MIT, and fits squarely within the Schwarzman College of Computing’s emphasis on integrating artificial intelligence with the sciences. Kellis recalls it all getting started back in 2012 via the connection of postdocs, Elizabeth Gjoneska of the Tsai Lab and Andreas Pfennig from the Kellis Lab, who had met at a seminar. With similarly overlapping interests in how gene regulation, and specifically epigenomic differences, affect the workings and health of the brain, they and other members of the two labs kindled dialogues that soon brought the professors together.

“The collaboration kind of happened organically,” said Kellis, professor of computer science and head of MIT’s Computational Biology Group. “We found kindred spirits — folks who thought similarly but were extremely complementary in their expertise.”

Within two years, the labs had jointly published two major papers. One in Nature, part of a sweeping set of reports on epigenomics that Kellis helped lead, showed that highly analogous sets of gene misregulation signals in the hippocampus of mice and humans each revealed a strong role for the brain’s immune cells and processes in allowing Alzheimer’s disease to progress. The other paper, in Cell, showed that in order to rapidly express genes critical for experience to affect synaptic connections, neurons naturally employ double-strand breaks of their DNA. The team hypothesized that failure to repair these breaks increases with age and may also contribute to neurodegeneration.

Each paper demonstrated the power of their combined approach. Since then, the collaboration has grown significantly to encompass about half a dozen projects. In 2016, for instance, they earned a National Institutes of Health grant to determine the significant epigenomic differences afoot in major brain cell types in Alzheimer’s disease.

In the last year, Kellis and Tsai received an influx of several new NIH grants and philanthropic gifts, such as the one establishing the Alana Down Syndrome Center (see page 12), enabling them to substantially expand their efforts in Alzheimer’s, tackle new disorders, bring in new collaborators, include new types of experiments, and expand their mechanistic studies. Their new directions include Schizophrenia, Bipolar Disorder, Psychosis in Alzheimer’s Disease, Frontotemporal Dementia, Lewy Body Dementia, and healthy aging.

Importantly, each experiment is designed together, Kellis says. Knowing that the team combines the capabilities of each lab, the team can be more ambitious.

“We think in a different way than any one lab would think by itself,” Kellis said. “For instance, I wouldn’t have the guts to ask many of these things that we are asking, if it wasn’t for our close collaboration with Li-Huei’s lab.”

In the Alana Center, they will apply their team science approach to modeling and analyzing Down syndrome, looking to identify and dissect the unique genetic and molecular signals that explain how the presence of an extra chromosome 21 affects the brain.

And with the new NIH grants, they will ask a litany of questions such as why many people with Alzheimer’s develop psychotic symptoms as well, what are the unique molecular signatures that distinguish Alzheimer’s and other dementias, and how do specific genetic variations in non-coding DNA elevate risk for a number of neurodegenerative and neuropsychiatric disorders.

“How privileged I feel to work with the world’s best computational team,” Tsai said. “This is only possible at MIT.”
April 18

**Colloquium with Huizhong Tao, PhD, University of Southern California**

Huizhong Tao is an Associate Professor of Physiology and Neuroscience at the University of Southern California. Her lab studies topics including the development, structure and function in the visual and auditory cortex.

April 23

**2019 Picower Lecture with Karel Svoboda, PhD, HHMI Janelia**

Karel Svoboda is a Group Leader at HHMI’s Janelia Research Campus. His lab is working on the structure, function and plasticity of neocortical circuits, mostly in the context of somatosensation.

May 2

**Colloquium with Marcy MacDonald, PhD, Massachusetts General Hospital, Harvard Medical School**

Marcy McDonald is a professor of neurology in Harvard Medical School. Her laboratory utilizes genetic strategies to understand the key underpinnings of inherited brain disorders in cross-discipline collaborative studies. A major focus is Huntington’s disease.
OUR VISION
The Picower Institute is a community of scientists dedicated to understanding the mechanisms that drive learning and memory and related functions such as cognition, emotion, perception, and consciousness. Institute researchers explore the brain at multiple scales, from genes and molecules, to cells and synapses, to circuits and systems, producing novel insights into how disruptions in these mechanisms can lead to developmental, psychiatric, or neurodegenerative disease.

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EDITORIAL CONTRIBUTORS
David Orenstein and Anne Trafton

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

TOP ROW: Mark F. Bear, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Investigator, Howard Hughes Medical Institute (HHMI); Emery Brown, Edward Hood Taplin Professor of Computational Neuroscience and Health Sciences & Technology, The Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology; Gloria Choi, Samuel A. Goldblith Career Development Assistant Professor of Applied Biology, Department of Brain and Cognitive Sciences; Kwanghun Chung, Assistant Professor, Departments of Chemical Engineering and Brain and Cognitive Sciences, Institute of Medical Engineering and Science core faculty; Steven Flavell, Lister Brothers Career Development Assistant Professor of Neuroscience, The Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology; Myriam Heiman, Associate Professor of Neuroscience, Department of Brain and Cognitive Sciences, Broad Institute core member; Troy Littleton, Menicon Professor of Biology and Neuroscience, Departments of Biology and Brain and Cognitive Sciences.

BOTTOM ROW: Earl Miller, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences; Elly Nedivi, William R. (1964) & Linda R. Young Professor of Neuroscience, The Picower Institute for Learning and Memory, Departments of Brain and Cognitive Sciences and Biology; Mriganka Sur, Paul E. Newton Professor of Neuroscience, Director of The Simons Center for the Social Brain; Susumu Tonegawa, Picower Professor of Biology and Neuroscience, Departments of Brain and Cognitive Sciences and Biology, Investigator, Howard Hughes Medical Institute, Investigator and Director of the RIKEN-MIT Center for Neural Circuit Genetics; Li-Huei Tsai, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Director, The Picower Institute for Learning and Memory; Matthew Wilson, Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology, Associate Director, The Picower Institute for Learning and Memory; Weifeng Xu, Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences.