Picower Institute for Learning and Memory

The Picower Institute for Learning and Memory is a world-class focal point for research and education in the field of neuroscience, and learning and memory. Learning and memory are central to human behavior and the Picower Institute's research aims to understand the mechanisms underlying these cognitive functions at the molecular, cellular, brain circuit, and brain system levels. The Picower Institute's research extends to other higher-order cognitive phenomena intimately associated with learning and memory, such as attention, decision making, and consciousness.

Awards and Honors

Kwanghun Chung received the National Institutes of Health New Innovator Award.

Myriam Heiman received the Paul and Lilah Newton Brain Science Award and became the Latham Family Career Development Assistant Professor.

Troy Littleton took up the Menicon Chair in Neuroscience and received the Brain and Cognitive Sciences Award for Excellence in Postdoctoral Mentoring.

Earl Miller was elected to the American Academy of Arts and Sciences for 2017 and received both the Goldman-Rakic Prize for Outstanding Achievement in Cognitive Neuroscience and the Paul and Lilah Newton Brain Science Award.

Elly Nedivi was elected as a fellow of the 2016 American Association for the Advancement of Science.

Li-Huei Tsai received the Society for Neuroscience Mika Salpeter Lifetime Achievement Award.

Kay Tye received the Society for Neuroscience Young Investigator Award and the Freedman Prize for Exceptional Basic Research.

Tuan Le Mau, a graduate student in the Emery Brown laboratory, received a Legatum Center Fellowship.

Meg McCue, a graduate student in the Kwanghun Chung laboratory, received the Walle Nauta Award for Excellence in Graduate Teaching.

Amanda Vernon, a graduate student in the Myriam Heiman laboratory, received the Angus MacDonald Award for Excellence in Undergraduate Teaching.

Dheeraj Roy, a graduate student in the Susumu Tonegawa laboratory, received the Harold M. Weintraub Graduate Student Award.

Jinsoo Seo, a research scientist in the Li-Huei Tsai laboratory, received the 2016 Infinite Kilometer Award.

Scarlett Barker, a graduate student in the Kay Tye laboratory, received the Angus MacDonald Award for Excellence in Undergraduate Teaching.

Caitlin Vander Weele, a graduate student in the Kay Tye laboratory, won the Federation of American Societies for Experimental Biology's BioArt contest.

Research Breakthroughs

There were major research advances in Picower Institute faculty laboratories during the reporting period; these are summarized below.

Researchers in the Mark Bear laboratory recently devised a novel approach that may lead to treatments for the loss of vision in human amblyopia. This approach involves the temporary inactivation of the retinas with a local anesthetic, setting in motion changes in the brain that may enable a complete recovery from the debilitating effects of visual deprivation in early life. Research is currently under way in the laboratory to uncover the precise mechanism or mechanisms of this recovery, and to determine if this knowledge can be translated into new and better treatments in humans.

There is significant evidence that many mutations associated with autism and intellectual disability have in common the disruption of protein synthesis and associated synaptic plasticity through activation of metabotropic glutamate receptor 5 (mGluR5), and that modulation of mGluR5 may be a beneficial treatment. The Bear laboratory has demonstrated that genetically reducing beta-arrestin-mediated signaling, downstream of mGluR5 activation, ameliorates several of the synaptic and behavioral deficits observed in fragile X model mice and, therefore, may serve as a novel therapeutic target for the treatment of autism and related disorders.

Neuronal plasticity peaks early in life during critical periods and normally declines with age, but the molecular changes that underlie this decline are not fully understood. Using the mouse visual cortex as a model, research conducted in the Bear laboratory, in collaboration with groups at the University of Utah and University of Tokyo, found that activity-dependent expression of the neuronal protein Arc peaks early in life, and that loss of activity-dependent Arc expression parallels loss of synaptic plasticity in the visual cortex. Genetic overexpression of Arc prolongs the critical period of visual cortex plasticity, and acute viral expression of Arc in adult mice restores juvenile-like plasticity. These findings provide a mechanism for the loss of excitatory plasticity with age, and suggest that Arc may be an interesting therapeutic target for modulation of the malleability of neuronal circuits.

The Miriam Heiman laboratory has extended its application of a new method called synthetic lethal in the central nervous system (SLIC) to identify genes that enhance toxicity of the mutant huntingtin (mHTT) gene, identifying several new enhancers of this gene's toxicity that are promising therapeutic targets for Huntington's disease. The Heiman laboratory also performed profiling of the cell-type–specific mechanism of action of antipsychotic drugs in the mammalian brain and has identified key differences to glutamatergic signaling genes caused by different classes of these drugs.

The Troy Littleton laboratory discovered that Huntington's disease and Huntington disease-like 2 (HDL2) polyglutamine expansion disease proteins act through distinct toxic pathways within neurons. The Littleton laboratory also discovered that unregulated calcium influx into distinct glial cell populations can either excite or inhibit neurons, leading to epilepsy or paralysis, respectively.

For decades, it has been widely accepted that holding thoughts "in mind" (i.e., in working memory) depends on neurons that sustain their spiking activity; this is

arguably the most-studied neural correlate of a cognitive function. In the past year, the Earl Miller laboratory published a study that upended this idea. All previous studies averaged across multiple instances (trials) on the assumption that averaging simply improves the signal-to-noise ratio. The problem is that the brain doesn't average; it works in real time. The Miller laboratory used multiple-electrode recording and cutting-edge analytical techniques to examine how neural activity unfolds in real time. It turned out that sustained activity was an artifact of averaging. Instead, there are sparse and complex temporal dynamics that suggest that working memories are stored by a temporary change in connections between neurons, not by sustained spiking.

Although 60,000 people a year in the US alone undergo general anesthesia, no one knows why it renders you unconscious. The Miller laboratory, in collaboration with the Emery Brown laboratory, is conducting the first wide-ranging assessment of the effects of general anesthesia on cortical neurons and networks. This includes testing the hypothesis that researchers can wake an animal up from general anesthesia through deep brain stimulation. Preliminary data suggests that this is possible.

The Miller laboratory has also published a new theoretical paper that may overturn more dogma. Since the early days of modern neuroscience, it has been assumed that every neuron has one function. Researchers in the Miller laboratory have shown, with computational modeling, that many cortical neurons must be multifunctional. Without that, the brain lacks the power for complex thought. This hypothesis fits well with recent experimental observations designed to test it.

Activity-dependent synapse formation is a key aspect of Hebb's postulate that experience is stored in the brain as long-lasting changes in circuit connectivity. In Elly Nedivi's laboratory, researchers have shown that Cortical Plasticity Gene 15 (CPG15) acts as an experience-dependent positive "selector" for synapses through a direct interaction with AMPA-type glutamate receptors.

In the Nedivi laboratory, scientists have used in vivo three-color two-photon microscopy in mouse visual cortex to track spine initiation and stabilization, as well as recruitment of the synaptic scaffold postsynaptic density protein 95 (PSD-95) to nascent spines, showing unequivocally that the defining step in synapse and spine stabilization is recruitment of PSD-95 and that it is this step that is the target of activity-dependent selection.

Researchers in Mriganka Sur's laboratory have shown that neurons in the visual cortex, the posterior parietal cortex, and the frontal motor cortex have unique and surprising roles in the performance of visual decision tasks. Neurons in frontal motor cortex retain short-term memory of the task, and are crucial for both perception and performance.

The Sur laboratory has discovered a critical physiological substrate for brain dysfunction in Rett Syndrome, a devastating neurodevelopmental disorder. Mutant mice that model Rett Syndrome have a reduced excitatory, as well as inhibitory, drive to pyramidal neurons of the cortex, arising from reduced responses in one crucial type of inhibitory neuron.

Using optogenetic technology to label and manipulate memory engram cells, Tonegawa laboratory researchers showed that the cortical area 1 (CA1) region of the brain is essential for the function of social memory, involved in the recognition of individuals.

This is the first proof of the location of storage for social memory information in the brain and an important step in further studies on social disorders such as autism.

The Tonegawa laboratory published two papers in high-profile journals focusing on neuronal populations in the basolateral amygdala. These studies challenge the dogma regarding the function of amygdala neurons and their circuits, which control negative (such as fear) and positive (such as joy) valence behaviors and memories. These studies have implications for the future development of new therapies for emotional disorders such as depression and post-traumatic stress disorder.

The Tonegawa laboratory staff made a landmark discovery that sheds light on a fundamental question of neuroscience: how memory is consolidated from short-term memory to long-term memory. Tonegawa laboratory researchers showed that, in response to experience, memory information is actually stored in the hippocampus and the prefrontal cortex. Over time, the memory information of the prefrontal cortex "matures" and becomes the primary location for access to the memory information; memory information in the hippocampus "de-matures" and becomes unresponsive for memory recall.

The Tsai laboratory, in collaboration with Emery Brown and Ed Boyden, showed that different sensory modalities could be recruited to entrain gamma oscillations and reduce Alzheimer's disease–related pathology and impact cognition. The first scientific article describing the effects of sensory gamma entrainment on reducing amyloid and tau pathology was published in Nature in December 2016.

The Tsai laboratory, in collaboration with the laboratories of Ed Boyden and Alvaro Pascual-Leone, identified a noninvasive transcranial stimulation approach. This approach has been demonstrated to control the motor behavior of mice.

The Tsai laboratory continues to explore improved approaches to target epigenetic enzymes for the purpose of enhancing cognitive function. Researchers identified the HDAC2–Sp3 complex as a critical factor that specifically regulates the expression of genes involved in synaptic functions. The transcription factor Sp3 cooperates with the histone deacetylase HDAC2 to regulate synaptic function and plasticity in neurons.

A new study from Kay Tye's laboratory identified the neurons that give rise to a loneliness-like experience. Another study from the Tye laboratory shows that different populations of amygdala neurons projecting to different targets have distinct functions in routing information regarding positive or negative emotional associations during memory retrieval. Researchers in the Tye laboratory also demonstrated that inhibitory neurons from the lateral hypothalamus serve to disinhibit midbrain dopamine neurons and drive motivated behaviors in a context-dependent manner.

Another new study from the Tye laboratory identified the role of the projection between the amygdala and the prefrontal cortex in biasing split-second decisions made when faced with environmental cues that predict conflicting outcomes (rewards and punishments) that are simultaneously presented. An account of a technological breakthrough from a collaboration between the Tye laboratory and the Ting laboratory, describing the development of a temporally precise activity-dependent tagging system, was published recently.

The Xu laboratory demonstrated that PSD-95 controls postsynaptic ubiquitination and phosphorylation signaling pathways. Researchers in the Xu laboratory also demonstrated that rapid experience-dependent translation of neurogranin enables durable context memory encoding, dependent on the autism spectrum disorder–associated fragile X mental retardation protein.

Personnel

In addition to 14 faculty members, the Picower Institute consists of other researchers, students, technical staff, and administrative support personnel. More than 280 community members participated in Picower Institute activities during the reporting period: 14 faculty members, three visiting scientists or scholars, 81 postdoctoral associates, 61 undergraduates, 39 graduate students, 68 research and technical staff, and 16 administrative and service staff.

Items of note during the academic year included the following:

- John Maher, senior financial officer, April London, financial coordinator, and Veronica Vela, development assistant, left the Picower Institute. Three searches are under way for their replacements, and the positions should be filled in early fall 2017.
- Joshua Sarinana transitioned from program administrator and science writer to become communications manager and science writer in August 2016. There is an additional search under way to fill the vacant program administrator position.
- James deMelo was hired as laboratory manager supporting Matthew Wilson in December 2016, replacing Shea Levy.
- Jesse De Angelis was hired as an administrative assistant II to Myriam Heiman and Weifeng Xu in March 2017.
- Jean Achorn was hired as an administrative assistant II to Kay Tye and Steven Flavell in June 2017, replacing Amanda Deveau.

Resource Development

The Picower Institute has enjoyed impressive success over recent years and that trend continued in 2016. These successes reflect the faith of MIT's most generous alumni and friends, along with numerous corporations and foundations, in the Picower Institute's ability to make valuable use of private resources. Picower resource development efforts identified more than 200 collaborative funding opportunities, expanded the institute's newsletter outreach to 3,000 individuals worldwide, hosted individual visits with more than 84 prospective and current donors, and worked closely with Picower Institute faculty to draft 12 prize nominations and 15 new formal philanthropic proposals. Outright gift payments to the Picower Institute for FY2016 totaled more than $9 million; new philanthropic gifts and pledges totaled more than $3.7 million.

Because of the generous support from the JPB Foundation and the late Jeffry Picower, researchers at the Picower Institute for Learning and Memory have been able to continue their ambitious research efforts and ventures into groundbreaking and transformational

areas of neuroscience that will lead to new and effective cures for brain illnesses. Two new gift commitments, totaling $450,000, for the Junior Faculty Development Program have allowed the continued support of this mentoring and career development program. The Junior Faculty Development Program has been expanded to include the Picower Institute's two newest members, Dr. Emery Brown and Steve Flavell, who are invaluable additions to the Picower Institute's roster. In October 2016, the JPB Foundation launched a unique program at the Institute called the Picower Institute Catalyst Program (Catalyst Program) with a $1 million gift to catalyze research by removing researchers' anxieties, and part of their financial burden, to fund indirect costs for new grants. This specific support aims to diminish significantly the faculty burden of finding and paying for infrastructure costs, allowing investigators to direct their efforts toward securing more external support for their research, in the hope that the researchers would be more likely to produce meaningful results. In just a few months, this revolutionary program has already increased the number of foundation grant applications submitted and enabled additional external support to be secured. In FY2016, all three JPB-supported programs—the Picower Institute Innovation Fund (PIIF), the Junior Faculty Development Program, and the Catalyst Program have allowed the Picower Institute to support breakthroughs that can map the brain more accurately in three dimensions, understand how synapses encode learned information, and identify brain circuits and disruptions that are key to various brain illnesses. Investing in this basic research has the potential to save lives and result in both direct and indirect economic effects.

Other notable new commitments include a generous $1 million gift commitment from MIT Corporation member Jeffrey S. Halis '76, SM '76, and his wife, Nancy. The gift will support Alzheimer's disease research at MIT that is associated with the Aging Brain Initiative. Similarly, the Glenn Foundation for Medical Research has pledged a new three-year commitment of $3 million to the Paul F. Glenn Center for the Science of Aging Research at MIT. Professor Leonard Guarente of MIT's Department of Biology leads the center; Professors Li-Huei Tsai and Angelika Amon are co-directors. The center's goal is to attain a better understanding of aging and its relation to the brain; of neurodegenerative disorders, including Alzheimer's disease, dementia, and learning and memory impairment; and of adult stem cells. The Robert A. and Renee E. Belfer Family Foundation continues to support the institute's work through the Neurodegeneration Consortium, a collaborative enterprise to which renowned scientists from MIT, from the University of Texas MD Anderson Cancer Center, and from Baylor College of Medicine are contributing. This funding enables the investigation of new ways to slow, stop, or reverse the progression of Alzheimer's and other neurodegenerative diseases. Continued support from the Alana USA Foundation, Inc., has allowed Picower Institute investigators to expand their Down syndrome research efforts and work toward developing new treatment prospects for individuals with the condition. The Cure Alzheimer's Foundation also approved a second year of funding for an Alzheimer's research project partnership and a second $400,000 gift to MIT to help support the research into Alzheimer's disease by Picower Institute Director and Professor Li-Huei Tsai and Professor Manolis Kellis from the Department of Electrical Engineering and Computer Science. This new partnership is part of a larger nationwide consortium of researchers, the Collaboration to Infer Regulatory Circuits and to Uncover Innovative Therapeutic Strategies consortium, led by Professor Kellis. Moreover, a new partnership began with the Ludwig Family Foundation, with $630,000 in support of efforts to map the aged brain in collaboration with MIT Bioengineering Professor Ed Boyden.

Significant efforts and development resources have been directed to building a major cross-institutional health research initiative on brain aging and related cognitive decline, called the Aging Brain Initiative at MIT. This initiative is led by Picower Institute Director Li-Huei Tsai along with eight founding faculty members from different disciplines; it has gained support from MIT's senior leadership and has become a top priority of MIT's Campaign for a Better World. Major events to raise awareness and increase the visibility of the effort included an MIT Campaign Roadshow event in Hong Kong in December; an event hosted by Renate and MIT alumnus Alex Dreyfoos '54, "Conversations on Health," aboard their yacht, *Silver Cloud*, in September; presentations at dinners for MIT Corporation members in September and March; and a dinner held in Pasadena, CA, in November, hosted by MIT alumnus Sam Losh '54 for people interested in both learning more about the Aging Brain Initiative and in supporting it.

The Picower Institute also co-hosted the biannual A Day with MIT's Brains on Brains symposium headed by the Department for Brain and Cognitive Sciences, to raise awareness and thank individuals who have supported the institute's work. The event, which took place on May 1, included informative conversations on the varied approaches taken to, and the progress made in, understanding the brain in health and in sickness. The event was well attended (approximately 100 prospective and current donors were there) and resulted in many connections with potential donors and increased visibility for the Picower Institute. The morning began with faculty talks, followed by an open-table lunch with faculty and students organized by popular research themes. The afternoon had short, "lightning" talks from a number of graduate students and scientists, providing a great opportunity to experience the breadth of work that takes place inside the institute.

MIT alumnus David Emmes '76 and MIT alumnus Donald Mattes '67 and his wife Glenda pledged to leave major gifts to the Institute and Aging Brain Initiative. Additionally, many smaller gifts from dedicated donors have proven vital to the Picower Institute's mission of advancing brain research. New funds included two gift annuities totaling $220,000 from Professor Morris Weisfeld for Alzheimer's disease research, a renewed $50,000 gift to support Myriam Heiman's work on schizophrenia from MIT alumnus Eduardo Elejalde '70, and a new $40,000 gift in support of the Aging Brain Initiative from David Emmes '76.

Media Recognition

In the reporting year, Picower Institute faculty published 22 articles in hallmark science journals (*Science*, *Neuron*, *Cell*, *Nature*, *Nature Neuroscience*, *eLife*, and the *Proceedings of the National Academy of Sciences*). Picower faculty published in 59 peer-reviewed publications overall.

The Picower Institute issued 27 press releases in the reporting period, and various news sources reported research done at the Picower Institute 60 times. News on Picower Institute research appeared in major media outlets such as WBUR, NBC News, CNBC, the *New York Times*, *Scientific American*, *Forbes*, the BBC, PBS, the *Boston Globe*, *Smithsonian Magazine*, Radiolab, *Der Spiegel*, the *Guardian*, the *Telegraph*, the *L.A. Times*, the *Atlantic Monthly*, the *Financial Times*, *MIT Technology Review*, and *Discover* magazine.

Programs and Activities

The Picower Institute was founded on the premise that collaboration among disciplines is an integral component of its research philosophy. To facilitate these collaborative interactions, the Picower Institute follows a rigorous calendar of formal lectures, conferences, and workshops as well as other informal events. Activities are designed to bring Picower researchers and the MIT neuroscience community together with other neuroscientists and practitioners from the public and private sectors to exchange research findings, facilitate cross-disciplinary collaborations, and continue to explore the potential advances that research about learning and memory mechanisms in the brain offers to science and society. Ongoing programs and activities are described below.

Held annually, the Picower Lecture was named to recognize and honor the generous support of the Picower Foundation for neurosciences at MIT. Each lecture features work of a current leader in the area of brain research. This year's lecturer will be Fred "Rusty" Gage of the Salk Institute for Biological Studies, winner of the Christopher Reeve Research Medal and the Max Planck Research Prize. He will speak at the Picower Institute on October 16, 2017 (rescheduled from March 2016 because of snow).

The Picower Institute colloquia bring together the highest caliber of learning and memory researchers from universities throughout the world to share their findings and experiences with the MIT community and to create working relationships with members of the Picower Institute. During the past year, colloquia speakers included Erin Schuman of the Max Planck Institute for Brain Research, Dr. Attila Losonczy of Columbia University Medical Center, Dr. Sandeep "Bob" Datta of Harvard Medical School, Lisa Giocomo of Stanford University School of Medicine, Yasmin Hurd of the Icahn School of Medicine at Mount Sinai, and Jin Hyung Lee of Stanford University.

In the language of neuroscience, the term plasticity refers to the minute but crucial physical changes that take place in our synapses every time we learn, experience, or remember anything new. At the Picower Institute, "Plastic Lunch" refers to a monthly series of informal talks during the academic year that give postdoctoral associates and graduate students from across the Picower Institute a chance to share their latest, often prepublished, research with colleagues within the Building 46 community. The Plastic Lunch series provides an opportunity for participants to improve their presentation skills and also fosters collaborations and builds new relationships between laboratories and across disciplines.

An endeavor targeted to the Picower Institute's postdoctoral community provided resources to support activities that build community and enrich interactions between postdoctoral colleagues and future associates. The Postdoctoral Association, now a Building 46–wide association, continues to expand and make improvements in partnership with administration for the postdoctoral community. Throughout the past year, postdoctoral associates convened a series of informal talks, educational seminars, and social events that included all Building 46 postdoctoral associates.

A monthly Picower Institute faculty lunch, known as the Picower Power Lunch, allows faculty and guest speakers to informally relate recent research findings or to present a new idea. Each year, after the close of the academic year, the Picower Institute hosts an annual retreat for its community members. This year, the Picower Institute's retreat was held on

June 5 and 6, 2017. More than 150 Picower Institute members attended the event, which was held in South Yarmouth, MA, at the Red Jacket Beach Resort. The retreat included 10 speakers as well as 23 poster presentations, representing 13 Picower laboratories.

The Picower Institute hosted the annual fall symposium, whose topic was the neurobiology of neurological disease, on October 25. Renowned neurobiologists from around the world gathered at the Picower Institute to present their latest research findings and to discuss vulnerabilities in, and basic underlying mechanisms associated with, neurological disease, as well as molecular pathways that could potentially be targeted for therapeutic treatments. The event was well attended, with more than 300 registrants.

Additionally, a special event was held on March 7, 2017, to mark the donation of five works of art by MIT alumnus Todd Siler to the Picower Institute. Siler gave a lecture on his works, which explore the creative process and applied innovative thinking, to a crowd of 100.

Together with the School of Science, the Picower Institute continued the newly launched Aging Brain Seminar Series, a bimonthly seminar series focused on fundamental and translational aging brain research. This series is part of the growing Aging Brain Initiative at MIT and has the goal of bringing together bright minds to give talks that are focused on ideas, and on a wide range of brain aging subjects, to foster learning, inspiration and wonder—and to provoke conversations that matter. Among the Aging Brain seminar speakers were Rudolph Tanzi of Massachusetts General Hospital and Harvard Medical School, Dr. Bradley Hyman of Massachusetts General Hospital and Harvard Medical School, Aaron Gitler of the Stanford University School of Medicine, and Dr. Brad Dickerson of Massachusetts General Hospital and Harvard Medical School.

Research programs enabled by philanthropic support from the JPB Foundation and the Institute of Physical and Chemical Research (Japan) (RIKEN Institute) afforded the Picower Institute a truly unique research environment, with support for faculty, laboratory members, and administrative team. The programs included the Clinical Collaborative Fellowship, the Picower Neurological Disorder Research Fund, the Junior Faculty Development Program, the Symposium Fund, the Picower Institute Innovation Fund, the RIKEN-MIT Center for Neural Circuit Genetics, and the Catalyst Program.

Research Initiatives

RIKEN-MIT Center for Neural Circuit Genetics

Established in April 2008, the RIKEN-MIT Center for Neural Circuit Genetics is directed by Professor Susumu Tonegawa. Jointly sponsored by the RIKEN Brain Science Institute in Japan and by MIT, the center's researchers seek to fully understand the brain mechanisms underlying specific cognitive phenomena such as memory or emotion. The center investigates not only the properties of individual cells, cellular clusters, and brain systems, but also the functions generated by their communications, which are important for uncovering the fundamental mechanisms operating in the healthy brain and for understanding how these mechanisms go astray under disease conditions. The center uses an interdisciplinary approach, combining cutting-edge transgenic and viral vector techniques, in vivo multielectrode recording technology, optical and magnetic-imaging techniques, and behavioral studies. The agreement funds the activities of the center, mainly supporting the laboratory of Susumu Tonegawa.

Viral Gene Transfer Core

The Picower Institute, in partnership with the McGovern Institute for Brain Research and with the support of an anonymous donor, launched the Viral Gene Transfer Core in fall 2008. Rachael Neve, an internationally renowned expert in viral vector research, with more than 400 publications, assumed the directorship of the Viral Gene Transfer Core. A self-supporting service facility, the Viral Gene Transfer Core is a unique resource for MIT's neuroscience community; it also serves external academic researchers. Viral gene delivery is a powerful adjunct to transgenic mice for sophisticated manipulations of neuronal function. The core specializes in vectors for circuit-based behavioral studies and offers world-renowned retrograde viral vectors that are not available from any other facility. This technology allows research laboratories to answer, in a uniquely direct way, basic questions about how specific neuronal circuits contribute to brain function and behavior. The use of these viruses to understand memory and cognition is expected to provide the basis for new treatments of neurological and psychiatric disorders.

Induced Pluripotent Stem Cell Core Facility

The Induced Pluripotent Stem Cell Core Facility (iPS Core Facility), launched in November 2010 by the Picower Institute, integrates the various research goals of members of the Picower and McGovern Institutes and the Department of Brain and Cognitive Sciences to create human and animal cell models of diseases. The various laboratories have expertise and experience with different experimental protocols; when combined in a collaborative manner to the study of human cells, these protocols result in accelerated progress in this novel, dynamic, and competitive field. The advent of human iPS cells has heralded a new generation of clinical and basic research into human disorders. Patient-derived skin fibroblast cells are reprogrammed into iPS cells; these allow researchers to examine a wide variety of diseases directly in human cells in addition to studying gene variants in patient populations. This core facility has rapidly become essential to studies of autism, psychiatric diseases, Alzheimer's disease, and many neurodegenerative diseases. The facility is accessible to users at all hours with a keycard security system. Shared equipment is available with a sign-up reservation system. In FY2014, the iPS facility became a fee-for-service facility, and opened its doors for the first time to other MIT users and to users external to MIT.

The iPS Core Facility is equipped for the specialized production, maintenance, expansion, preservation, and distribution of human fibroblasts, iPS cell lines, neuronal progenitor cells derived from iPS and embryonic stem (ES) cells, iPS- and ES-derived neurons, induced neuronal cells, and neural organoids. The iPS Core Facility has approximately 1,250 square feet of space in three tissue culture areas; one room is dedicated for viral work with iPS and ES cells, under the Biosafety Level 2+ protocol, and two tissue culture areas are for maintenance, expansion, and general handling of non-viral work–related iPS and ES cell cultures under the Biosafety Level 2 protocol. There are 10 biosafety cabinets, 16 carbon dioxide incubators, one three -gas incubator that allows control of the oxygen concentration, and bench areas. There are also four biosafety cabinets equipped with microscopes for the observation and handling of cells in a clean and protected environment. Currently, the iPS Core Facility has produced more than 70 patient-specific iPS cells from patients with schizophrenia, bipolar disorder, depression, Rett syndrome, Alzheimer's disease, and Down syndrome; a healthy person's skin fibroblasts serve as controls. The number of cell lines and iPS cells continues to rise.

Tak Ko, the supervisor of the iPS Core Facility, has also set up an orientation program and trainings to educate faculty and potential users on the facility's use. The iPS Core Facility provides a powerful incentive for different laboratories to collaborate and exchange ideas. Since its inception, the facility has been used by more than 25 researchers at MIT. Collaborations with researchers outside MIT have been continuing, with noteworthy interactions with the Broad Institute of MIT and Harvard and firms in the biotech industry. Many prominent articles have been accepted by and published in various journals, including *Nature Neuroscience*, *PLoS One*, and *Molecular Psychiatry*, on the basis of data obtained using the iPS Core Facility.

Bioinformatics Core Facility

Bioinformatics is a branch of biological science that deals with the study of methods for storing, retrieving, and analyzing large sets of biological data. In March 2012, a bioinformatics core facility at the Picower Institute for Learning and Memory was established to primarily provide computational support to investigators there for studying neurological diseases. The bioinformatics core facility has been constructed to utilize high-performance computing clusters for high-throughput quantitative data analysis, with particular focus on analyzing genomic and epigenomic data generated from human brain and blood tissues, iPS cell–based in vitro models, and rodent-based in vivo models. Since April 2015, the facility provides workshops to the Brain and Cognitive Sciences community that are tailored to teaching the basics on use and applicability of current genomics and epigenomics software to graduate students and postdoctoral associates. Hosted by Picower bioinformatician Fan Gao, the workshops highlight different themes, ranging from next-generation genomic DNA profiling, transcriptomic profiling (RNA-Seq), and transcription factor/histone code profiling (ChIP-Seq) to protein network analysis and visualization. The goal is to teach participants how to use publicly available resources for bioinformatics data processing, analysis, and visualization. Since March 2016, the facility has also provided an in-house neural-bioinformatics database and several web-based bioinformatics tools to the MIT neuroscience community.

CLARITY Core Facility

In 2015, a new shared equipment facility for clear lipid-exchanged anatomically rigid imaging/ immunostaining-compatible tissue hydrogel (CLARITY) imaging was created. The facility, and the imaging technique, allow the Picower Institute to lead in the field of brain mapping microscopy methods to make advances and delve into unexplored areas of neuroscience research. The facility includes hardware and software infrastructure for the CLARITY technology. The equipment includes a high-content rapid throughput imaging microscope system from Leica Microsystems and Leica supporting software. The facility has been in heavy use, with the Chung, Sur, Tsai, Tye, Nedivi, Tonegawa, and Xu laboratories the primary users to date; however, the equipment is available to all Picower laboratories, 24 hours a day, 7 days a week. Videos and data collected using this new technology are shown at Brain Lunch, Plastic Lunch, the winter brain conference, and will also be shared at upcoming Gordon Conferences and the Society of Neuroscience conference. Most notable are videos depicting clarified mouse and human patient postmortem brains, which show new pathological information for diseases such as Alzheimer's disease.

The Aging Brain Initiative

Since the summer of 2014, significant efforts and resources have been directed to the launching of a major cross-institutional health research initiative on brain aging and related cognitive decline: the Aging Brain Initiative at MIT. This initiative is led by Picower Institute Director Li-Huei Tsai, the Dean of MIT's School of Science, Michael Sipser, and eight other founding faculty members from different disciplines. The Aging Brain Initiative has gained senior leadership support, including becoming a top priority of MIT's Campaign for a Better World. The bold goals of this program are to begin a transformative process of collaborative study, discovery, and rapid integration of brain-aging research into real-world applications, and to establish a long-term investment platform to address this global health imperative. The program aims to bring MIT's leading memory and neurobiology researchers, together with representatives of other disciplines, including engineers, computer scientists, economists, urban planners and social policy experts, into a single cohesive group with clinicians and industry partners to think creatively about brain-aging needs and to collectively tackle ambitious ideas that have not otherwise been pursued. High-risk flagship projects, created across a diverse range of expertise, include a whole-systems-level perspective extending beyond the traditional clinical pathology and genetic approaches of today to include vital aspects of the challenge, such as understanding memory loss and developing smart home technologies for improved care. Frequent multidisciplinary discussion forums and seminars enable open sharing of data and accelerated pollination of ideas for growth into new areas.

In the first five years of the Aging Brain Initiative, efforts will be focused on a four-pronged approach that consists of project-based and team-based, immediately implementable research to help us understand both healthy and unhealthy brain aging, and to develop real-world solutions that can reduce cognitive decline, aid home care, and point toward a cure for diseases such as dementia. Specifically, the initiative's leaders plan to identify biomarkers of aging, develop circuit-specific therapeutics, personalize approaches to treatment, and uncover the secrets to healthy aging. In December 2016, the team published a breakthrough discovery and description of a potential non-invasive therapy for Alzheimer's disease, and in May 2017, they published on a new non-invasive deep-brain stimulation technology that has major implications for Parkinson's disease and amyotrophic lateral sclerosis.

Faculty Research Summaries

Picower Institute faculty research areas and AY2017 accomplishments are below.

Mark Bear

Mark Bear is Picower Professor, Professor of Neuroscience, Department of Brain and Cognitive Sciences. Researchers in Bear's laboratory took the question of how the brain is modified by experience, deprivation, and disease as a guide to their work. Their overarching interest was in the question of how experience and deprivation modify synaptic connections in the brain. Experience-dependent synaptic plasticity is the physical substrate of memory; it sculpts connections during postnatal development to determine the capabilities and limitations of brain functions, is responsible for the reorganization of the brain after damage, and is not only vulnerable in numerous psychiatric and neurological diseases but also contributes to their symptoms.

Historically, the Bear laboratory's major efforts to address this question have been focused on the visual cortex and hippocampus. The visual cortex is a site of robust experience-dependent synaptic plasticity, exemplified by the consequences of temporary monocular deprivation during childhood. Monocular deprivation sets in motion a stereotyped choreography of synaptic modification whereby the deprived eye's inputs to visual cortex rapidly lose strength and, with a delay, the open eye's inputs undergo a compensatory gain in strength. The behavioral consequence of this plasticity is severe visual impairment in the deprived eye. In humans, this condition is called amblyopia, and it is responsible for loss of vision in more than 1% of the world population. Thus, the visual cortex is an excellent preparation in which to connect the elementary molecular mechanisms of synaptic plasticity to their behavioral consequences. Further, insights into how synapses are depressed or potentiated have potential clinical applications for the treatment of amblyopia.

The hippocampus is a cortical structure that is critical to forms of learning and memory. The simple cellular architecture of the hippocampus also makes it amenable to electrophysiological investigations of synaptic plasticity that are much more difficult in other parts of the brain. In the early 1990s, researchers in the Bear laboratory applied insights gained from a theoretical analysis of synaptic plasticity to establish a phenomenon called homosynaptic long-term depression (LTD). LTD is the functional inverse of long-term synaptic potentiation (LTP). Although LTD and LTP are expressed at synapses throughout the brain, they are particularly robust at the Schaffer collateral synapses in the CA1 region of the hippocampus. The hippocampus is therefore an excellent preparation in which to dissect the molecular basis of bidirectional synaptic plasticity. Insights gained here can not only be applied to synaptic modifications elsewhere in the brain, but they are also relevant to understanding the basis of hippocampus-dependent memory storage and diseases of cognition.

In the course of studying LTD, researchers made a discovery that has turned out to have major therapeutic significance for human developmental brain disorders that cause autism. One form of hippocampal LTD is triggered by activation of metabotropic glutamate receptor 5 (mGluR5) and requires immediate translation of messenger RNAs (mRNAs) at synapses. In the course of studying this type of synaptic plasticity, protein synthesis (and LTD) downstream of mGluR5 was found to be exaggerated in the mouse model of fragile X. Human fragile X retardation, caused by the silencing of the fragile X mental retardation 1 gene, is the most common inherited form of intellectual disability and autism. Insight gained by the study of LTD suggested that exaggerated protein synthesis downstream of mGluR5 might be pathogenic and contribute to many symptoms of the disease. Subsequent tests of the so-called mGluR theory have shown that inhibition of mGluR5 can correct multiple mutant phenotypes in animal models of fragile X, ranging from mouse models to fruit fly models. Human clinical trials were initiated on the basis of the strength of this science, and results to date indicate that treatments can be developed to benefit this patient population substantially. The mGluR theory has contributed to a major paradigm shift away from the historic view that genetic diseases of brain development are untreatable to the modern view that such diseases may be ameliorated or corrected with appropriate therapy.

Current work in the laboratory is focused on two related themes: mechanisms and regulation of naturally occurring synaptic plasticity in visual cortex, and

pathophysiology and treatment of genetically defined developmental brain disorders. Researchers in the Bear laboratory primarily study mouse models, using a broad range of methods that include, but are not limited to, brain slice electrophysiology and biochemistry, in vivo electrophysiology, two-photon functional and structural imaging, and behavioral analysis. The Bear laboratory is question oriented rather than method oriented; laboratory members will apply any technology that is needed to address the questions of greatest interest.

Emery Brown

Emery Brown is Edward Hood Taplin Professor of Medical Engineering; Professor of Computational Neuroscience; Member, Institute for Data, Systems, and Society; Core Faculty, Institute for Medical Engineering and Science; Warren M. Zapol Professor of Anaesthesia, Massachusetts General Hospital; and Co-Director, Health Sciences and Technology Program. This year Professor Brown delivered the 2017 Severinghaus Award Lecture at the American Society of Anesthesiologists meeting and a 2017 Medallion Lecture at the Joint Statistical Meeting. The Brown laboratory also published two important papers this past year.

The first paper showed that it is possible to bring rats out of general anesthesia by optogenetic stimulation of dopamine neurons in the ventral tegmental area in the midbrain. The results give a precise mechanism to explain the previously reported results that intravenous administration of methylphenidate induces reanimation from general anesthesia in rodents, most probably through a dopaminergic mechanism. This work has laid the groundwork for a phase II clinical trial in humans to test the administration of methylphenidate to induce emergence from general anesthesia. If the trial is successful, this may make regular use of methylphenidate a way to wake patients up from general anesthesia and to mitigate the postoperative dysfunction that is commonly seen in elderly patients after surgery.

The second paper suggested that auditory or visual stimuli at 40 Hz decrease amyloid load in a rodent model of Alzheimer's disease. In addition, this 40 Hz stimulation is associated with behavioral improvement. The results suggest that either auditory or visual stimulation at 40 Hz may be a therapy for Alzheimer's disease in humans.

Kwanghun Chung

Kwanghun Chung is Samuel A. Goldblith Professor of Applied Biology, Assistant Professor of Chemical Engineering, Assistant Professor of Brain and Cognitive Sciences, and Core Faculty, Institute for Medical Engineering and Science. Professor Chung's laboratory has an interdisciplinary research team that is devoted to developing and applying novel technologies for holistic understanding of large-scale complex biological systems. In the past year, his group has continued to develop their recent technologies (System-Wide control of Interaction Time and kinetics of Chemicals [SWITCH], magnified analysis of the proteome [MAP], stochastic electrotransport) to accelerate the pace of scientific discovery and development of therapeutic strategies in a broad range of biomedical research. Recent research advances by the Chung laboratory include advancing their SWITCH three-dimensional imaging to reveal network-specific amyloid progression and subcortical susceptibility related to Alzheimer's disease. Professor Chung was named a 2016 National Institutes of Health New Innovator awardee. He has

traveled extensively, including to Seoul National University and Yale University, as well as to Vlaams Instituut voor Biotechnologie (VIB) and Gordon research conferences, to speak about his group's technologies and their applications.

Professor Chung taught subjects 10.302 Transport Processes and HST.562[J] Pioneering Technologies for Interrogating Complex Biological Systems. He also served on the IMES Committee for Academic Programs, as well as the IMES graduate admission and faculty search committees. Professor Chung has recently founded a start-up, LifeCanvas Technologies, which hopes to advance the adoption and use of Chung laboratories technologies developed at MIT.

Steven Flavell

Steven Flavell is Picower Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences.

Action potentials and synaptic transmission occur over the time scale of milliseconds, yet the brain generates behaviors that can last seconds, minutes, or hours. A major goal of neuroscience is to understand how neural circuits generate coherent behavioral outputs across such a wide range of time scales. Sustained behavioral states—including arousal states (sleeping, waking) and complex internal states (emotions)—are thought to be controlled by biogenic amine and neuropeptide neuromodulators. However, there is still a poor understanding of the basic neural mechanisms that underlie behavioral state initiation, maintenance, and termination. Moreover, it is unclear how external and internal cues, such as satiety status, alter the outputs of the neural circuits that control these states. The goal of Steven Flavell's laboratory is to understand how neural circuits generate sustained behavioral states, and how physiological and environmental information is integrated into these circuits.

Steven Flavell's recent studies have identified a neuromodulatory circuit that generates two opposing behavioral states in *Caenorhabditis elegans*. He used quantitative behavioral analyses paired with genetics to show that serotonin and the neuropeptide pigment dispersing factor each act to initiate and extend one behavioral state while inhibiting the other state, resulting in a flip-flop switch that determines state stability. He performed in vivo calcium imaging and optogenetics (channelrhodopsin) to examine the temporal relationship between neuromodulation and behavioral transitions. Finally, he identified the exact neurons within the *C. elegans* connectome that make up this neuromodulatory circuit. This work demonstrated how neuromodulation supplements fast motor circuits with slow temporal dynamics, organizing behaviors into long-lasting states.

Steven Flavell is now using his expertise in this area to ask fundamental questions about how behavioral states are generated and how environmental cues influence state generation, including:

- What circuit-wide patterns of activity define the stable configurations for each behavioral state? How are these patterns stabilized by neuromodulators such as serotonin? Toward this end, the Flavell laboratory has constructed a microscope that is suitable for whole-brain calcium imaging and is using this new technology to characterize large-scale neural activity patterns associated with distinct behavioral states.

- How do neural circuits detect the feeding/satiety status of an animal, so that only certain behavioral states are generated while food is available? The Flavell laboratory has recently identified a conserved family of ion channels that may mediate satiety sensing by neurons, and is now completing the characterization of these new channels.

- How do animals compare current food levels with those of the recent past and adjust behavior accordingly? The Flavell laboratory has taken advantage of new cell-specific molecular profiling methods to examine how gene expression changes in animals with different feeding experiences. Surprisingly, they found that the chemoreceptors for smell and taste show striking expression changes in response to changes in nutritional state. The laboratory is now characterizing the molecular pathways that drive these changes, and examining the impact of these changes on neural activity and behavior.

Researchers in the Flavell laboratory have also expanded their studies to examine more broadly how animals coordinate and structure their behavior. They built a set of microscopes that can record *C. elegans* animals for their entire lifespans and developed machine vision approaches to automatically quantify every behavior generated by an animal. This technology will soon be coupled to the whole-brain calcium imaging approach outlined earlier. By linking large-scale neural activity to a comprehensive understanding of behavioral structure, this work should provide fundamentally new insights, revealing how the brain generates a structured and coordinated set of behavioral outputs.

Myriam Heiman

Myriam Heiman is Latham Family Career Development, Associate Professor of Neuroscience, Department of Brain and Cognitive Sciences.

The most common neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and Huntington's disease, display distinct clinical presentations. The basis of these distinct clinical presentations is the enhanced vulnerability of certain neuronal types to death or dysfunction. Researchers in the Heiman laboratory are broadly interested in this phenomenology of enhanced vulnerability in neurodegenerative disease, viewing it as an opportunity to discover valuable insights into the cell biology of each disease-relevant neuronal cell type and to identify new therapeutic targets. The Heiman laboratory is using innovative approaches to address these questions of selective vulnerability, which have remained open questions in the field for decades. In the past year, cell type-specific molecular profiling studies in Huntington's disease models have revealed that:

- There is a broad loss of cell type-specific marker genes, accompanied by an up-regulation of genes usually not expressed in neurons, that occurs early in Huntington's disease model progression;

- The neurons thought to be most vulnerable in Huntington's disease have the highest level of early-stage disease progression gene expression changes in response to mutant Huntingtin (mHTT), including many genes that are linked to oxidative stress responses; and

- There is a broad expansion of constitutive heterochromatin in neurons that occurs in the presence of mHTT, an expansion that has been linked to loss of key transcription factor function.

These data on the earliest gene expression changes in Huntington's disease models together provide strong evidence for transcriptional dysregulation as a contributive driver of, rather than a secondary response to, mHTT toxicity. Next, using the laboratory's novel genome-wide in vivo SLIC screening methodology, researchers have identified a number of promising modifiers of mHTT neuronal toxicity in pathways previously implicated in Huntington's disease and in several novel targets. These results provide a rich data set for many future studies aimed at identifying new therapeutic targets to modulate mHTT toxicity in vivo.

Members of the Heiman laboratory have also performed extensive molecular profiling of neuronal subtypes under chronic administration of both typical and atypical antipsychotic drugs that are used to treat schizophrenia. These studies have uncovered a core molecular signature of approximately 100 genes whose expression is altered in neurons upon chronic treatment with any typical or atypical antipsychotic drug. As expected, this gene set is highly enriched in genes whose products function at the glutamatergic postsynaptic density. Surprisingly, however, it has been observed that only clinically relevant doses of the drug clozapine, considered to be the superior atypical antipsychotic drug, induce transcriptional alterations only in certain subtypes of schizophrenia-relevant neurons, unlike all other antipsychotic drugs. It is hoped that these findings can be used for future rational antipsychotic drug design.

Troy Littleton

Troy Littleton is Menicon Picower Professor of Neuroscience, Professor of Biology, Departments of Biology and Brain and Cognitive Sciences.

The focus of the Troy Littleton laboratory's work is to understand how neuronal synapses form, function, and undergo plasticity. To complement these studies, members of the Littleton laboratory also study how alterations in neuronal signaling contribute to several brain diseases, including epilepsy, autism, and Huntington's disease. Researchers combine molecular biology, protein biochemistry, electrophysiology, and imaging approaches with *Drosophila* genetics to address these questions. Despite the dramatic differences in complexity between *Drosophila* and humans, genomic and functional analyses have confirmed that key neuronal proteins and the mechanisms they govern are remarkably similar. Researchers are therefore attempting to elucidate the pathways that mediate neuronal signaling and how they are disrupted in disease, using *Drosophila* as a model system.

Recent progress in the Littleton laboratory includes new insights into the polyglutamine diseases as well as into how glial cells contribute to neuronal excitability. Huntington disease-like 2 and Huntington's disease are adult-onset neurodegenerative diseases characterized by movement disorders, psychiatric disturbances, and cognitive decline. Huntington's disease is the most common inherited polyglutamine expansion disorder, but how mutant Huntingtin or HDL2 (encoding a polyglutamine repeat in a junctophilin antisense mRNA) disrupts neuronal function is unclear. In particular, it is unknown what subcellular compartment pathogenic Huntingtin acts within, and whether the pathogenesis is associated with aggregated or more soluble forms of the protein. Using a *Drosophila* Huntington's disease model, researchers found that non-aggregated pathogenic Huntingtin acts locally at synaptic terminals to disrupt endosomal

trafficking of synaptic growth receptors, leading to aberrant wiring defects. Genetic manipulations to increase endosomal trafficking from signaling endosomes, or to reduce bone morphogenetic proteins (BMP) signaling, reduces pathology in this Huntington's disease model. These data indicate that pathogenic Huntingtin can act locally within nerve terminals to disrupt synaptic endosomal signaling and induce neuropathology. In contrast to Huntingtin aggregates that are exclusively cytoplasmic in *Drosophila*, HDL2 forms large nuclear aggregates, with only smaller puncta observed in the cytoplasm. Altering localization of HLD2 with the addition of a nuclear localization or nuclear export sequence demonstrates that nuclear accumulation is required for toxicity in the *Drosophila* HDL2 model. Directing HDL2 to the nucleus exacerbates toxicity in multiple tissue types; confining HDL2 to the cytoplasm restores viability to control levels. These data indicate that although HD and HDL2 have similar clinical profiles, distinct pathogenic mechanisms are likely to drive toxicity in Drosophila models of these disorders.

The regulation of excitatory and inhibitory balance is critically important to neuronal circuit output. Mounting evidence indicates that glial cells are key regulators of neuronal activity. Researchers recently found that *Drosophila* cortex glia exhibit near-membrane microdomain calcium ion (Ca^{2+}) oscillatory activity, similar to that observed in mammalian glia. They identified mutations in Zydeco, a glial-specific potassium ion (K^{+})–dependent sodium ion/calcium ion (Na^{+}/Ca^{2+}) exchanger that eliminated microdomain Ca^{2+} oscillations in cortex glia and led to higher intracellular Ca^{2+} levels. This increase in cortex glial Ca^{2+} leads to enhanced seizure susceptibility, as does acute induction of Ca^{2+} influx through ectopic expression of transient receptor potential channels in cortex glia. These observations suggest a model in which an increased Ca^{2+} influx into cortex glia leads to neuronal hyperexcitability. However, it is unknown whether *Drosophila* astrocytes also exhibit Ca^{2+} activity and whether astrocyte Ca^{2+} signals have a similar role in exciting neighboring neurons.

In a recent study, *Drosophila* astrocytes were found to exhibit spontaneous, microdomain calcium cation transients, resembling those observed in their mammalian counterparts. Surprisingly, unlike cortex glia, acute calcium cation influx in astrocytes causes behavioral paralysis and a rapid loss of neuronal activity. This suppression of neuronal activity is caused in part by rapid endocytosis of the gamma-aminobutyric acid (GABA) transporter (GAT) from astrocyte membranes, leading to enhanced GABA levels in the synaptic cleft. Researchers identified the Rab11 protein as a key regulator of GAT trafficking downstream of astrocyte calcium cation influx, and found that reduction in GAT turnover via suppression of Rab11 function ameliorates the induced suppression of neuronal activity. The data provide new insights into astrocyte calcium cation signaling and indicate that distinct glial subtypes in the Drosophila brain can mediate opposing effects on neuronal excitability.

Earl Miller

Earl Miller is Picower Professor, Professor of Neuroscience, Department of Brain and Cognitive Sciences. The overarching goal of Miller's laboratory is to understand cognitive functions in a broader context, as a product of interactions between networks and circuits of neurons, brain areas, and systems. To this end, the Miller laboratory has developed (and shares) technology and techniques for recording from many separately movable,

acutely inserted electrodes. Such recording allows the gap between the global scope of human brain imaging and the spatiotemporal precision of single-neuron physiology to be bridged. It also allows examination of precise timing relationships and interactions between neuronal populations. The laboratory couples this with investigating the kind of sophisticated, flexible behaviors at which humans and monkeys are so adept.

In the past year, the Miller laboratory has made discoveries that suggest that rhythmic synchrony between neurons (brain waves) plays an important role in consciousness and learning. They found that when animals learn new categories, there are increases in brain wave synchrony between cortical areas. Researchers have also been finding that loss of consciousness may occur when anesthesia hyper-synchronizes neurons to slow brain waves, preventing normal communication. This all suggests that brain waves play a major role in regulating neural communication.

Elly Nedivi

Elly Nedivi is William R. (1964) and Linda R. Young Professor of Neuroscience, Professor of Biology, Departments of Brain and Cognitive Sciences and Biology. The Nedivi laboratory 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. After identifying a large number of candidate plasticity genes (CPGs), researchers have elucidated the neuronal and synaptic function of two previously unknown CPGs, CPG15 and CPG2, and have shown that each provides unique insight into diverse aspects of plasticity mechanisms. Both molecules have subsequently become well known; CPG15 (later named neuritin) is known as an extracellular ligand with multiple roles, including roles outside the nervous system, and CPG2 is known as a product of SYNE-1, one of the most reliable genetic indicators of bipolar disorder. Motivated by the large number of CPGs that affect neuronal structure, the Nedivi laboratory has a long-standing collaboration with Peter So's laboratory in the Department of Mechanical Engineering to develop multiphoton microscopy for large-volume, high-resolution imaging of dendritic arbor and synaptic structural dynamics in vivo. Recently, this effort has developed methods for labeling and chronic monitoring of excitatory and inhibitory synapses across entire neuronal arbors in the mouse visual cortex in vivo.

Mriganka Sur

Mriganka Sur is Paul E. (1965) and Lilah Newton Professor, Professor of Neuroscience, Department of Brain and Cognitive Sciences. Sur's laboratory studies the development, plasticity, and dynamics of the cerebral cortex. An important goal is to use insights from brain development to understand mechanisms of developmental brain disorders. The laboratory's discoveries in fiscal year 2017 included three major findings.

Mapping specific sensory features to future motor actions is a crucial capability of mammalian nervous systems. Perceptual decision making involves both processing sensory information and mapping that information onto appropriate motor commands via learned sensorimotor associations. Researchers investigated the role of the primary visual cortex, posterior parietal cortex, and frontal motor cortex for sensorimotor mapping in mice during performance of a memory-guided visual discrimination task. Wide-

scale imaging of neuronal populations in each of these regions revealed that neurons exhibited heterogenous responses spanning all epochs of the task. Population analyses demonstrated unique encoding of stimulus identity and behavioral choice information across regions, with the primary visual cortex encoding the stimulus, the frontal motor cortex encoding choice even early in the trial, and the posterior parietal cortex multiplexing the two variables. Optogenetic inhibition during behavior revealed that all regions were necessary during the stimulus epoch, but only frontal motor cortex was required during the delay and response epochs. Stimulus identity could thus be rapidly transformed into behavioral choice, requiring primary visual cortex, posterior parietal cortex, and frontal motor cortex during the transformation period, but only frontal motor cortex for maintaining the choice in memory prior to execution. To explore the role of each region more fully, researchers examined the activity of neurons in primary visual cortex and posterior parietal cortex during passive viewing and engaged behavior. Unlike neurons in primary visual cortex, which responded robustly to stimuli in both conditions, most neurons in posterior parietal cortex responded exclusively during task engagement. However, posterior parietal cortex responses were heterogeneous, with a smaller subset of neurons exhibiting stimulus-driven, contrast-dependent responses in both conditions. To test whether posterior parietal cortex responses primarily encoded the stimulus or the learned sensorimotor contingency, researchers took images of the same neurons before and after retraining mice on a reversed task contingency. Unlike neurons in primary visual cortex, most neurons in posterior parietal cortex exhibited a dramatic shift in selectivity after retraining and reflected the new sensorimotor contingency. Mouse posterior parietal cortex is therefore strongly task-dependent, contains heterogeneous populations sensitive to stimulus and choice, and plays an important role in the flexible transformation of sensory inputs into motor commands.

Rett Syndrome: Control of early human neurogenesis by MeCP2-regulated micro-RNAs

Rett syndrome (RTT) is an X-linked neurodevelopmental disorder caused primarily by mutations in the methyl-CpG-binding protein 2 (MECP2) gene, which encodes a multifunctional epigenetic regulator with known links to a wide spectrum of neuropsychiatric disorders. The effects of MECP2 on early brain development are unclear. Researchers in the Sur laboratory employed isogenic human RTT patient-derived iPS cell and methyl CpG binding protein 2 (MeCP2) short hairpin RNA knockdown approaches to identify novel MeCP2-regulated microRNAs (miRNAs) enriched during early human neuronal development. Focusing on the most dysregulated miRNAs, laboratory members found two targets—miR-199 and miR-214—that are increased during early brain development to differentially regulate extracellular signal regulated kinase (ERK)/mitogen-activated protein kinase and protein kinase B (PKB/AKT) signaling. Inhibiting the expression of microRNA precursors miR-199 or miR-214 in iPS cell–derived neural progenitors deficient in MECP2 restored AKT and ERK activation, respectively, and ameliorated the observed alterations in neuronal differentiation. Moreover, overexpression of miR-199 or miR-214 in wild-type mouse embryonic brains was sufficient to disturb neurogenesis and neuronal migration in a manner similar to that seen in MECP2 knockdown. Taken together, the data support a novel miRNA-mediated pathway downstream of MECP2 that influences neurogenesis via interactions with central molecular hubs linked to autism spectrum disorders.

Circuit alterations in the pathophysiology of Rett Syndrome

Rett syndrome is known to arise from loss of function mutations in MECP2 in the brain, but fundamental aspects of its physiological mechanisms are unresolved. By whole-cell recording of synaptic responses in visual cortex of MECP2-mutant mice in vivo, Sur laboratory members showed that visually driven excitatory and inhibitory conductances were both reduced in cortical pyramidal neurons. The ratio of excitation to inhibition was increased in amplitude and prolonged in time course. These changes predict circuit-wide reductions in response reliability and selectivity of pyramidal neurons to visual stimuli, as confirmed by two-photon imaging from MECP2–mutant mice. Targeted recordings revealed that parvalbumin-expressing inhibitory interneurons in mutant mice had reduced responses. Parvalbumin-specific MECP2 deletion alone substantially recapitulated effects of global MECP2 deletion on cortical circuits, including reduced pyramidal neuron responses and reduced response reliability and selectivity. Furthermore, MECP2 mutant mice showed reduced expression of the chloride cotransporter KCC2 and a reduced ratio of KCC2 to the sodium-potassium-chloride cotransporter NKCC1. Perforated patch recordings demonstrated that the reversal potential for GABA was more depolarized in mutant mice, but was restored by application of the NKCC1 inhibitor bumetanide. Treatment with recombinant human insulin-like growth factor 1 restored responses of parvalbumin-expressing and pyramidal neurons, including their reliability and selectivity, and increased KCC2 expression to normalize the KCC2/NKCC1 ratio. Thus, loss of MECP2 in the brain alters both excitation and inhibition in brain circuits via multiple mechanisms. Loss of MECP2 from a specific interneuron subtype contributes crucially to the cell-specific and circuit-wide physiological deficits of RTT. The joint restoration of inhibition and excitation in cortical circuits is pivotal to functional correction of the disorder.

Susumu Tonegawa

Susumu Tonegawa is Picower Professor, Professor of Neuroscience, Professor of Biology, Departments of Biology and Brain & Cognitive Sciences. Tonegawa's laboratory continues to seek to decipher the brain mechanisms underlying memory and its disorders. During the past year, the Tonegawa laboratory made the following major discoveries:

- The brain areas responsible for the storage of social memory are the ventral hippocampus and the nucleus accumbens.
- Neuronal populations in the basolateral amygdala that control positive and negative valence behaviors and emotions are spatially segregated.
- Memory information is stored in two brain locations upon experience.
- A memory "matures" through consolidation of this information from one area, for short-term recall, to the other, for long-term recall.

Ventral CA1 neurons store social memory

The medial temporal lobe, including the hippocampus, has been implicated in social memory. However, it remains unknown which parts of these brain regions and their circuits hold social memory. Researchers were able to show that ventral hippocampal

CA1 neurons of a mouse and their projections to a nucleus accumbens shell play a necessary and sufficient role in social memory. Both the proportion of activated ventral hippocampal cells and the strength and stability of the responding cells are greater in response to a familiar mouse than to a previously unencountered mouse. Optogenetic reactivation of ventral hippocampal neurons that respond to the familiar mouse enabled memory retrieval and the association of these neurons with unconditioned stimuli. Thus, ventral hippocampal neurons and their nucleus accumbens shell projections are a component of the storage site of social memory.

Antagonistic negative and positive neurons of the basolateral amygdala

The basolateral amygdala is a site of convergence of negative and positive stimuli and is critical for emotional behaviors and associations. However, the neural substrate for negative and positive behaviors and relationship between negative and positive representations in the basolateral amygdala are unknown. Tonegawa laboratory members were able to identify two genetically distinct, spatially segregated populations of excitatory neurons in the mouse basolateral amygdala that participate in valence-specific behaviors and are connected through mutual inhibition. These results identified a genetically defined neural circuit for the antagonistic control of emotional behaviors and memories.

Basolateral to Central Amygdala Neural Circuits for Appetitive Behaviors

Basolateral amygdala principal cells are capable of driving and antagonizing behaviors of opposing valence. Basolateral amygdala neurons project to the central amygdala, which also participates in negative and positive behaviors. However, the central amygdala has primarily been studied as the site for negative behaviors, and the causal role for central amygdala circuits underlying appetitive behaviors is poorly understood. Researchers in the Tonegawa laboratory have identified several genetically distinct populations of central amygdala neurons that mediate appetitive behaviors and dissect the basolateral amygdala-to-the-central-amygdala circuit for appetitive behaviors. Protein phosphatase 1 regulatory subunit 1B+ basolateral amygdala pyramidal neurons to dopamine receptor 1+ central amygdala neurons defines a pathway for promoting appetitive behaviors, while R-spondin 2+ basolateral amygdala pyramidal neurons to dopamine receptor 2+ central amygdala neurons defines a pathway for suppressing appetitive behaviors. These data reveal genetically defined neural circuits in the amygdala that promote and suppress appetitive behaviors, analogous to the direct and indirect pathways of the basal ganglia.

Engrams and circuits crucial for systems consolidation of a memory

Episodic memories initially require rapid synaptic plasticity within the hippocampus for their formation and are gradually consolidated in neocortical networks for permanent storage. However, the engrams and circuits that support neocortical memory consolidation have thus far been unknown. Researchers in the Tonegawa laboratory found that neocortical prefrontal memory engram cells, which are critical for remote contextual fear memory, were rapidly generated during initial learning through inputs from both the hippocampal–entorhinal cortex network and the basolateral amygdala. After their generation, the prefrontal engram cells, with support from hippocampal memory engram cells, became functionally mature with time. Although hippocampal

engram cells gradually became silent with time, engram cells in the basolateral amygdala, which were necessary for fear memory, were maintained. These data provide new insights into the functional reorganization of engrams and circuits underlying systems consolidation of memory.

Li-Huei Tsai

Li-Huei Tsai is Picower Professor, Professor of Neuroscience, Department of Brain and Cognitive Sciences.

Multi-sensory gamma stimulation for Alzheimer's disease

Gamma oscillatory activity is important for higher-order cognitive functions and has been shown to be altered in Alzheimer's disease. Researchers in the Tsai laboratory had previously reported that gamma entrainment mediated by a non-invasive light flicker at 40 Hz reduced amyloid load and morphologically transformed microglia in the visual cortex of Alzheimer's disease mouse models. Laboratory members have now designed a non-invasive 40 Hz click-train to induce gamma entrainment through auditory stimulation. Following 40 Hz auditory stimulation, a marked reduction in amyloid load and tau phosphorylation was found in Alzheimer's disease mouse models and the Tau P301S mouse model, respectively, in both auditory cortex and hippocampus. The findings in the hippocampus are striking, as the Tsai laboratory had previously reported that 40 Hz visual flicker did not impact amyloid levels or microglia in this brain region, which is both critical for memory formation and one of the earliest brain regions affected in Alzheimer's disease. In addition to changes in microglia morphology, researchers also discovered that 40 Hz auditory stimulation resulted in an astrocyte response and blood vessel dilation. Chronic auditory stimulation significantly improved spatial and recognition memory in the 5XFAD mouse model. Finally, the effects of concurrent light flicker and auditory stimulation were tested. In addition to the primary sensory cortex and hippocampus memory center, Tsai laboratory members also examined the medial prefrontal cortex, which is known to be involved in high-order cognitive functions such as working memory. Either light flicker or auditory stimulation alone failed to induce effects in the medial prefrontal cortex; however, concurrent stimulation of both visual and auditory senses at 40 Hz reduced amyloid levels and elicited a striking microglia response in the medial prefrontal cortex. These results reveal that gamma entrainment can be achieved via different sensory modalities to evoke wide-ranging effects on Alzheimer's disease–associated pathology and to improve cognitive function. Moreover, propagation of these effects to other brain regions, including the medial prefrontal cortex, is best achieved through concurrent stimulation.

Noninvasive Deep Brain Stimulation via Temporally Interfering Electric Fields

Deep brain stimulation has been effective in helping patients with disorders such as Parkinson's disease and obsessive-compulsive disorder, and it also has great potential for other disorders, such as depression and Alzheimer's disease. However, as deep brain stimulation is a surgical procedure, it bears the potential for complications that limit its deployment. In addition, cognitive impairment and dysarthria are common adverse effects of deep brain stimulation that could be eliminated with a more focal mode of neural stimulation. Non-invasive brain stimulation methods, such as

transcranial magnetic stimulation and transcranial electrical stimulation, have been used in many human clinical and neuroscientific investigations, but these techniques achieve only transient stimulation and have limited focality at depth. Researchers in the Tsai laboratory recently reported a novel noninvasive strategy for electrically stimulating neurons at depth. By delivering two electric fields at slightly different carrier frequencies, which are themselves too high to recruit effective neural firing but for which the offset frequency is low enough to drive neural activity, it is possible to create an electric field envelope at the offset frequency. This low-frequency modulated electric field can cause neurons to be electrically activated at a deep focus, without driving neighboring, or overlying, brain regions. Laboratory members validated the concept of temporal interference via modeling and physics experiments, and verified that neurons in the living mouse brain could follow the electric field envelope. They also demonstrated the utility of temporal interference stimulation by stimulating neurons in the hippocampus of living mice without recruiting neurons of the overlying cortex. The work also showed that, by altering the currents delivered to a set of immobile electrodes, experimenters can steerably evoke different motor patterns in living mice. This non-invasive, steerable, three-dimensional focal brain stimulation method has the potential to transform the risk–benefit ratio for deep brain stimulation by providing an alternative without the need for surgery. More, the ability to deliver stimulation with focality at depth is a significant improvement over the precision of procedures such as transcranial magnetic stimulation and transcranial electrical stimulation, and procedures like them. Such a stimulator may enable millions of patients suffering with drug-resistant brain disorders to be non-invasively treated, relieving their suffering.

Identification of a critical negative regulator of histone deacetylase in AD and other neurodegenerative diseases

Epigenetic regulators such as histone deacetylases (HDACs), which remove acetylation from histones, are critical players in the functions of neurons. Previous work had shown that inhibiting HDAC2, which has a negative role in neuronal plasticity and synaptic gene expression and is up-regulated in Alzheimer's disease patients and mouse Alzheimer's disease models, could help alleviate Alzheimer's disease–related cognitive impairment. However, despite repeated efforts to identify small molecules to target HDAC2, there is no current compound that can specifically inhibit HDAC2. In the Tsai laboratory's most recent work, researchers utilized an integrative genomics approach to identify proteins that mediate HDAC2 recruitment to synaptic plasticity genes. They identified the interaction of transcription factor Sp3 with HDAC2 as a critical factor for HDAC2 to mediate its negative effect on synaptic function. Like HDAC2, Sp3 expression was elevated in Alzheimer's disease patients and mouse models. Moreover, reduction of Sp3 not only ameliorated synaptic dysfunction, but mere exogenous expression of an HDAC2 fragment containing the Sp3 binding domain also restored synaptic plasticity and memory in a mouse model with severe neurodegeneration. These findings indicate that targeted disruption of HDAC2–Sp3 interaction with small molecules could serve as a viable therapeutic target to improve impaired cognition in Alzheimer's disease patients.

Kay Tye

Kay Tye is Whitehead Career Development Professor, Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences. Since Tye's arrival at the

Picower Institute in January 2012, she has been working to identify the circuit and synaptic mechanisms underlying emotional processing and motivated behaviors, in both health and disease, in rodent models. The long-term objective is to identify common circuit perturbations that may underlie comorbidity between psychiatric disease states such as addiction, anxiety, and depression. To do this, the Tye laboratory employs an interdisciplinary approach, integrating electrophysiological, optogenetic, pharmacological, and imaging techniques to study the neural bases of behavior. More recently, Tye laboratory researchers have identified a population of dopamine neurons in the dorsal raphe nucleus that underlie the experience of social isolation. It is a real challenge to identify ensembles of neurons that participate in complex behaviors that may be intermingled with neurons of distinct functions; to meet it, the Tye laboratory has developed a temporally precise, activity-dependent tool that allows the expression of any transgene (opsins, fluorescent proteins, calcium indicators, and so on) when neurons that have elevated calcium levels are illuminated. Researchers in the Tye laboratory hope to connect the mesolimbic dopamine system with the amygdalar glutamatergic network and identify common pathways that may underlie multiple behavioral phenotypes relevant to anxiety, addiction, and depression.

Matthew A. Wilson

Matthew A. Wilson is Sherman Fairchild Professor, Professor of Neuroscience, Professor of Biology, Departments of Brain and Cognitive Sciences and Biology. Work in Wilson's laboratory continues to focus on the role of the hippocampus in the formation, maintenance, and use of memory in the mammalian nervous system during awake and sleep states. In previous experiments, researchers in the Wilson laboratory have shown that the hippocampus reactivates memories of recent experience during sleep in what may be described as the animal correlate of dreaming. They have demonstrated that the reactivation of specific memories can be triggered through the use of auditory cues, effectively "engineering" dream content, providing the means to establish the causal relationship between memory processing during sleep and subsequent awake behavior. They have also found that hippocampal memory reactivation that occurs while animals stop briefly on a maze to '"think" is paired with information about anticipated rewards, providing insights into potential mechanisms of goal-directed planning and decision making. Using optogenetic approaches to manipulate neural activity, they have identified novel circuits involved in the regulation of attention and sleep, as well as demonstrating the role of brain rhythms in enhancing memory performance.

Weifeng Xu

Weifeng Xu is Picower Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences. Researchers in the Xu laboratory study how experience shapes the excitatory circuit connectivity, using a combination of molecular, cellular biological, electrophysiological, and behavioral analyses in the rodent model system to study critical players in synaptic plasticity and learning and memory. The mechanisms are associated with diseases such as autism, schizophrenia, bipolar disorder, and mental retardation. The overarching goal is to understand the molecular mechanisms for experience-dependent, long-lasting modification of excitatory circuit connectivity, which is critical for information processing and storage in the brain.

Signaling Scaffold for Synaptic Plasticity

The specificity of signal transduction from neurotransmitter release to intracellular signaling cascades is critical for information encoding in the brain. Synaptic scaffold proteins orchestrate the signal transduction via organizing different protein networks. The overall landscape of how different scaffold proteins control the synaptic content is being drawn by mapping the synaptic content using quantitative proteomic and phosphoproteomic approaches. Researchers in the Xu laboratory found that manipulations of the membrane-associated guanylate kinase family protein PSD-95 lead to profound changes in the tyrosine phosphorylation of selected targets. This finding provides novel insight into how synaptic receptors are regulated through this post-translational modification. Additionally, manipulation of PSD-95 causes significant shifts in postsynaptic content, notably ubiquitination ligase adaptor proteins, which target and activate the ubiquitin-proteosome degradation pathway, suggesting that PSD-95 regulates synapse stability via ubiquitination. These findings provide a comprehensive view of the signaling networks important for experience-dependent modification of synaptic connectivity.

Regulation of Calcium Homeostasis in Experience-dependent Plasticity and Learning and Memory

Calcium is essential for activity-dependent neural plasticity in the brain. The cellular response from calcium influx is normally mediated via calcium-binding protein, calmodulin-dependent processes. Neurogranin, a calmodulin-binding protein, is centrally localized in principal neurons throughout the cortex and hippocampus at the subcellular region where calcium-dependent signaling is essential for synaptic plasticity. The neurogranin gene has been associated with neurological and neuropsychiatric disorders, including schizophrenia and mental retardation.

Researchers found neurogranin to be rapidly translated upon novel context exposure. Activity-dependent translation of neurogranin contributed to the adrenergic facilitation of protein synthesis-dependent LTP and contextual memory formation. Fragile X mental retardation protein interacts with the three prime untranslated region (3'-UTR) of neurogranin and is required for activity-dependent translation of neurogranin in the synaptic compartment and contextual memory formation. Together, the results of work in the Xu laboratory reveal that rapid local neurogranin translation regulated by fragile X mental retardation protein in the hippocampus during memory acquisition is required for durable context memory encoding through the adrenergic facilitation of LTP.

Li-Huei Tsai
Director
Picower Professor of Neuroscience