

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, 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 systems levels. The Picower Institute's research also extends to other higher-order cognitive phenomena that are intimately associated with learning and memory, such as attention, decision making, and consciousness.

Awards and Honors

Picower Professor of Neuroscience Mark Bear received the 2015 IPSEN Foundation Neuronal Plasticity Prize and an Inscopix Deciphering Circuit Basis of Disease (DECODE) Award.

Assistant Professor Kwanghun Chung received a Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative Award from the National Institutes of Health (NIH).

Assistant Professor Myriam Heiman received an NIH Exceptional, Unconventional Research Enabling Knowledge Acceleration (EUREKA) Award.

Picower Professor of Neuroscience Earl Miller received a Professional Achievement Award from the Kent State University Alumni Association in 2015; he was named an Amar G. Bose Research Fellow in 2014.

Professor Elly Nedivi received a BRAIN Initiative Award from NIH.

Newton Professor of Neuroscience Mriganka Sur received inaugural BRAIN Initiative awards from both NIH and the National Science Foundation (NSF). Sur is the only researcher to receive both prestigious awards.

Whitehead Career Development Assistant Professor Kay Tye was among Technology Review's "Top 35 Innovators under 35." She also received the New York Stem Cell Foundation Neuroscience Robertson Investigator Award, the Department of Brain and Cognitive Sciences (BCS) Award for Excellence in Undergraduate Advising, the Harold E. Edgerton Faculty Achievement Award, the Award for Outstanding Undergraduate Research (UROP) Faculty Mentor, and a McKnight Scholar Award.

Rebecca Canter was named an MIT Graduate Woman of Excellence.

Sun-Yun Kim was awarded the Donald Lindsley Prize in Behavioral Sciences and was named a Simons Fellow of Life Sciences.

Xu Liu and Steven Ramirez received the 2014 American Ingenuity Award.

Steven Ramirez was named one of National Geographic's Emerging Explorers.

Mette Rathje received the Sapre Aude Award for Young Research Talent from the Danish Council of Independent Research.

Laura Stoppel was named an MIT Graduate Woman of Excellence.

Research Breakthroughs

Major research advances in Picower Institute faculty laboratories during the report period are summarized below.

Researchers in Mark Bear's laboratory showed that two very different genetic causes of autism and intellectual disability disrupt protein synthesis at synapses, and that a treatment developed for one disease produced a cognitive benefit when used to treat the other. The researchers zeroed in on how the brain forms memories of what has been seen. They showed that a form of visual recognition memory is stored in the primary visual cortex through mechanisms of synaptic plasticity. Impairments in detecting and recognizing familiar visual elements and patterns are features of a number of neuropsychiatric disorders, including autism and schizophrenia.

Heiman laboratory researchers have found a master regulator of the transcriptional dysregulation that is seen in Huntington's disease, a complex called PRC2. Altering PRC2 activity in mice leads to a mimic of Huntington's disease in otherwise normal mice. The Heiman laboratory has also developed a new method, called synthetic lethal in the central nervous system (SLIC), for exploring the links between aging and neurodegenerative diseases.

The Littleton laboratory discovered that patients with a rare neuromuscular disorder and those with nerve damage tied to autoimmune disorders may share the same faulty synapses.

Researchers in Earl Miller's laboratory have proven that the brain's cortex does not process specific tasks in highly specialized modules—showing that the cortex is, in fact, quite dynamic when sharing information.

The Miller laboratory discovered that neurons hum at different frequencies to tell the brain which memories it should store. The researchers found that two brain regions that are key to learning—the hippocampus and the prefrontal cortex—use two different brain-wave frequencies to communicate as the brain learns to associate unrelated objects. Whenever the brain correctly links the objects, the waves oscillate at a higher (beta) frequency; when the guess is incorrect, the waves oscillate at a lower (theta) frequency.

Researchers in Mriganka Sur's laboratory have shown that release of the neurotransmitter acetylcholine, which accompanies attention and arousal, activates a highly specific inhibitory–disinhibitory circuit in the cortex, causing neuronal activity to desynchronize and enhancing the information content of spike trains. The Sur laboratory also identified a fundamental property about cortical neurons: inhibitory neuron functionality is not an immutable property of cortical cells, but a consequence of more complex network dynamics.

Researchers in Li-Huei Tsai's laboratory showed that each time a person learns something new, brain cells break their DNA, creating damage that the neurons must immediately repair. This process of DNA breakage that allows the human brain to learn and to generate new memories also leads to degeneration with advancing age.

Researchers in the Tsai laboratory have identified a master genetic regulator, miRNA-137, that could account for faulty brain functions that contribute to schizophrenia and could be a new target for treatment.

An interdisciplinary team co-led by Picower director Li-Huei Tsai and Manolis Kellis, a professor in MIT's Computer Science and Artificial Intelligence Laboratory, showed that susceptibility to Alzheimer's disease (AD) is rooted in the brain's immune system. The research also identified new therapeutic targets for AD and suggests that the decreased neuron function that is a hallmark of the disease is not caused by genetic predisposition but is, rather, a consequence of exposure to environmental factors and aging, as well as of interactions with the altered immune function.

Using optogenetic technology to label and manipulate memory engram cells, researchers in Susumu Tonegawa's laboratory discovered two neural circuit pathways that act in competition to dictate the emotional aspect of an episodic memory experience.

The Tonegawa laboratory made a landmark discovery that overturns previously assumed knowledge about amnesia and the neural mechanism for memory retention. Tonegawa researchers used optogenetic and memory engram manipulation technology and showed that memories remain intact even in an amnesic state, meaning that memory failure is caused by retrieval failure rather than storage failure. They showed that memory is retained in specific connections between multiple cellular ensembles that are activated by learning. They also showed that protein synthesis-dependent long-term potentiation is unnecessary for the retention of a memory but underlies the efficient recall of a memory.

The Tonegawa laboratory also showed that the optogenetic activation of a cellular ensemble holding positive memory information was sufficient to alleviate depression-like symptoms in mice. This discovery has significant implications for the future treatment of depression in humans.

A new study from Kay Tye's laboratory showed that a neural circuit that controls compulsive feeding is separate from circuits that control hunger-driven feeding. Another study from the Tye laboratory shows that different populations of amygdala neurons project to different targets and thereby mediate positive and negative associative memory formation and approach and avoidance. This study also characterized the electrophysiological, morphological, and transcriptomic profiles of these cell populations.

The Xu laboratory has found a causal connection between a well-known synaptic protein, PSD-95, and the duration of traumatic memories.

Personnel

In addition to 12 faculty members, the Picower Institute consists of other researchers, students, and technical and administrative support personnel. More than 240 community members participated in Picower Institute activities during the report

period: 12 faculty members, two visiting scientists/scholars, 48 postdoctoral associates, 70 undergraduate students, 26 graduate students, 65 research and technical staff, and 18 administrative and service staff.

Items of note during the academic year included the following:

- Constantinos Zahariadis was hired as administrative support for Dr. Tsai in September 2014.
- Jiyoun Won was hired as administrative support for Headquarters in January 2015.
- David Vaughn, assistant director for administration, and Alicia Mackin, program administrator, left the Picower Institute. Two searches are under way for their replacements; it is expected that the positions will be filled during fall 2015.

Resource Development

Raising the resources that enable the faculty and students in the Picower Institute to carry on their work continues to be a high priority. In fiscal year 2015, many Picower Institute faculty members gave freely of their time for meetings with donors and potential donors. Resource development efforts also identified more than 110 collaborative funding opportunities and worked closely with Picower Institute faculty to draft 17 prize nominations and 10 new philanthropic proposals. New philanthropic gifts and pledges for FY15 totaled more than \$22.4 million.

Thanks to the generous support provided from the JPB Foundation and the Jeffrey Picower Bequest, the researchers at the Picower Institute for Learning and Memory have continued their ambitious research efforts and ventures into high-risk, high-reward areas of neuroscience that might otherwise have been left unexplored. Two new transformational gift commitments—a three-year, \$9.9 million gift for the Picower Institute Innovation Fund and a three-year gift of \$9 million for a Junior Faculty Development Program (JFDP)—have allowed the continued support of the high-risk innovation program. The gifts also support the expansion of this program to include new engineering collaboration awards with faculty from outside the Picower Institute, new structures to foster a positive neuroscience community experience, long-term career success for junior faculty, and work toward the mission of the Picower Institute.

Six main programs now stem from these funding sources, supporting a truly unique research environment with support for Institute faculty, laboratory members, and administrative team. The programs include, in addition to the JFDP, the MIT-MGH Clinical Fellowship Program, the Picower Neurological Disorder Research Fund, the Symposium Fund, and the Picower Institute Innovation Fund (PIIF). Additionally, although the majority of funds has been allocated directly to research, in fiscal year 2015 the PIIF and the JFDP have allowed the Picower Institute to support specialized technical expertise and build common-use core facilities in biostatistics, human stem cell work, and the three-dimensional clear lipid-exchanged anatomically rigid imaging/immunostaining-compatible tissue hydrogel (CLARITY) process. CLARITY brain

mapping microscopy that will strategically help researchers to make new advances and delve into unexplored areas of neuroscience research.

Other notable new commitments include a generous \$1.7 million gift and pledge from Brazil's Alana Foundation that enables collaborative study of the links between Down syndrome and Alzheimer's disease. The gift—\$1.7 million to the Picower Institute and \$1.7 million to Case Western Reserve University—will fund a series of joint studies led by Li-Huei Tsai, director of the Picower Institute, and Alberto Costa of the Case Western Reserve University School of Medicine with a focus on developing effective new therapies. Similarly, the Whitehall Foundation, the Alfred Sloan Foundation, and the New York Stem Cell Foundation have supported several individual Picower faculty with new gifts totaling \$1.9 million for research in learning and memory.

Since the summer of 2014, significant efforts and development resources have been directed to the launching of 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 six other founding faculty members from different disciplines; it has gained the support of senior leadership and has become a top priority of the School of Science. On June 3, Dean Michael Sipser chaired an advisory council meeting on the effort to help with strategic planning for support. Two proposals under consideration would support these research efforts and individual meetings with high-net-worth individuals are actively being pursued.

On May 4, together with the Department of Brain and Cognitive Sciences, the Picower Institute co-hosted the biannual Brains on Brains Symposium to provide an opportunity to confer with its most generous donors and to showcase the range of groundbreaking work of Picower Institute faculty and others in BCS. The event was exceptionally well attended (with approximately 200 registrants) and resulted in several new commitments to the department fellowship program. The day concluded with an intimate dinner hosted by Dean Sipser and Department Head Jim DiCarlo at the Catalyst restaurant to cultivate relationships and pay tribute to members of the departmental Visiting Committee.

New leadership gifts included additional funds in support of work on autism in the Bear laboratory. Several smaller annual gifts were also received from alumni and friends, particularly for discretionary work on Alzheimer's disease, neuropsychiatric research, and Down syndrome research.

Media Recognition

The Picower Institute has attained a distinguished international reputation as a leader in neuroscience research. The scholarly excellence of faculty members is reflected in their publication records. In the reporting year, Picower Institute faculty members published 33 articles in hallmark science journals (Science, Neuron, Cell, Nature, Nature Neuroscience, and the Journal of Neuroscience) and in 83 peer-reviewed publications overall.

The Picower Institute issued 30 press releases in the reporting period. Articles appeared in major broadcast and print media, such as BBC News, WBUR, Huffington Post, Forbes, TIME Magazine, The New Yorker, Science News, USA Today, The Washington Post, Smithsonian magazine, The Boston Globe, CBS News, Reuters, and The Wall Street Journal. Picower Institute research breakthroughs were also broadcast via the web on Science20.com, Mirror.co.uk, Independent.ie, Heraldscotland.com, ScientificAmerican.com, Sciencecodex.com, Boston.com, Presstv.ir, Dvice.com, and WBUR.org, among others.

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 such 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 Institute 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 explore the potential that research advances about learning and memory mechanisms in the brain offer to science and society. Ongoing programs and activities are described below.

Held annually, the Picower Lecture was named to honor and recognize the generous support of the Picower Foundation for the neurosciences at MIT. Each lecture features the work of a current leader in the area of brain research. This year's lecturer was Dr. Yadin Dudai from the Weizmann Institute of Science in Israel. His talk, entitled "The First Seconds of Episodic Memory, and the Years Thereafter" took place on April 30, 2015.

The Picower Institute Colloquia series brings the highest caliber of researchers in learning and memory from universities throughout the world to share their findings and experiences with the MIT community as well as to create working relationships with members of the Picower Institute. During the past year, colloquia speakers were Dr. Rafael Yuste of Columbia University, Dr. Daniel Choquet of the University of Bordeaux, Dr. Susan Sesack of the University of Pittsburgh, Dr. Ege Kavalali of the University of Texas Southwestern Medical Center, Dr. Sacha Nelson of Brandeis University, and Dr. Ming Guo of the University of California, Los Angeles.

In the language of neuroscience, "plasticity" refers to the minute but crucial physical changes that take place in the brain's synapses every time we learn, experience, or remember anything new. At the Picower Institute, "Plastic Lunch" refers to a biweekly series of informal talks during the academic year that give postdoctoral researchers and graduate students from across the Picower Institute a chance to share their latest, often pre-published, research with colleagues in 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 across disciplines and between laboratories.

An endeavor aimed at 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 for the postdoctoral community in partnership with administration. Throughout the past year, the association convened a series of informal talks, educational seminars, and social events that include all Building 46 postdoctoral researchers.

A monthly Picower Institute faculty lunch, known as the Picower Power Lunch, allows faculty and guest speakers to informally relate recent research findings or present a new idea. Each year, after the close of the academic year, the Picower Institute hosts an annual retreat for its community members. The eighth annual Dana and Betty Fisher Retreat of the Picower Institute for Learning and Memory was held on June 15th and 16th, 2015. More than 160 Picower Institute members attended the event held in Falmouth, Massachusetts, at the Seacrest Resort. The retreat included 10 speakers and presentations and 17 posters from Picower Institute laboratories.

In May 2015, together with the School of Science, the Picower Institute launch a new 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. Its goal is to bring together bright minds to give talks that are idea-focused, and on a wide range of subjects on brain aging, to foster learning, inspiration, and wonder—and to provoke conversations that matter.

Research Initiatives

RIKEN-MIT Center for Neural Circuit Genetics

The RIKEN-MIT Center for Neural Circuit Genetics, established in April 2008, is directed by Professor Susumu Tonegawa. Jointly sponsored by the RIKEN Brain Science Institute in Japan and by MIT, the Center for Neural Circuit Genetics seeks to understand fully 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. These are important for uncovering the fundamental mechanisms operating in the healthy brain and for understanding how these mechanisms go astray in the presence of disease. 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 between the RIKEN Brain Science Institute and MIT funds the activities of the center, supporting the laboratory of Susumu Tonegawa. Two more laboratories, to be run by faculty members not yet hired, will be funded in the future.

Viral Vector Core Facility

The Viral Vector Core Facility was launched in fall 2008 by the Picower Institute, in partnership with the McGovern Institute for Brain Research, with the support of an anonymous donor. Dr. Rachael Neve, an internationally renowned expert in viral vector

research, with more than 250 publications, assumed the directorship of the facility. A self-supporting service facility, the Viral Vector Core Facility is a resource for MIT's neuroscience community; it is also available to others, outside and across MIT. Viral gene delivery is a powerful adjunct to transgenic mice for sophisticated manipulations of neuronal function. The facility initially offered modified herpes simplex virus for delivery of genes into neurons in the brain; this resource is not available anywhere else in the world. This technology allows research laboratories to answer, in a direct way, basic questions about how specific types of neurons contribute to brain function and behavior. The use of these viruses to understand memory and cognition will provide the basis for new treatments of neurological and psychiatric disorders.

Induced Pluripotent Stem Cell Core Facility

The Picower Institute launched the Induced Pluripotent Stem Cell (iPS) Core Facility in November 2010. The facility integrates the various research goals of members of the Picower Institute, the McGovern Institute, 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 which, when combined in a collaborative manner and applied to the study of human cells, can result in accelerated progress in this novel, dynamic, and competitive field. In FY14, the iPS Core Facility became a fee-for-service facility, and opened its doors for the first time to other MIT users and to users outside MIT.

The iPS Core Facility has produced more than 50 patient-specific iPS cells from patients with schizophrenia, bipolar disease, depression, Rett syndrome, Alzheimer's disease, and Down syndrome, and from a healthy person's skin fibroblasts as controls. Tak Ko, the supervisor of the facility, has also set up workshops and trainings to educate faculty members and potential users on the types of work that they can do at the facility. This common 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 20 researchers at MIT. Collaborations with researchers outside MIT have been increasing, with noteworthy interactions with the Broad Institute and with the biotech industry. Many prominent articles have been published in peer-reviewed journals based on data obtained at the iPS Core Facility and MIT researchers have used the capabilities of the iPS Core Facility as leverage to receive external funding on numerous occasions.

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 was established, primarily to provide computational support to institute investigators for studying neurological diseases. The bioinformatics facility was constructed to utilize high-performance computing clusters for high-throughput data analysis, with particular focus on genomic and epigenomic data analysis. Since April 2015, the facility has provided workshops, hosted by Picower bioinformatician Dr. Fan Gao, that are tailored to teaching the basics of the use and applicability of current genomics and epigenomics software to graduate students and post-doctoral researchers in the entire BCS community. Workshops highlight different themes, ranging from next-generation genomic DNA profiling, transcriptomic profiling,

transcription factor/histone code profiling sequencing (Chip-seq), and three-dimensional genome analysis 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.

CLARITY Core Facility

This past year, a new, shared CLARITY imaging equipment facility was created to allow the Picower Institute to lead in brain mapping microscopy methods to make new advances and delve into unexplored areas of neuroscience research. The facility includes hardware and software infrastructure for the CLARITY technology, with training workshops in CLARITY imaging provided by Picower Professor Kwanghun Chung. The equipment includes a high-content, rapid-throughput imaging microscope system and supporting software from Leica Microsystems. The facility has been in heavy use; the primary users to date are researchers from the Chung, Sur, Tsai, and Tye laboratories. However, the equipment is available to all Picower laboratories and is available for use 24 hours a day, seven days a week. Videos and data collected using this new technology have been shown at Brain Lunch, Plastic Lunch, and the Winter Conference on Brain Research, and will also be shared at upcoming Gordon Research Conferences. Most notable are videos that depict clarified postmortem mouse and human brains showing new information on the pathology of diseases such as Alzheimer's and Parkinson's. An additional real-time polymerase chain reaction machine is included in the facility for supplementary gene expression analysis by the Picower community.

The Aging Brain Initiative

Since the summer of 2014, significant efforts and development resources have been directed to the launching of a major cross-institutional health research initiative on brain aging and related cognitive decline. Called the Aging Brain Initiative at MIT, the initiative is led by Picower director Li-Huei Tsai along with six other founding faculty members from different disciplines; it has gained the support of senior leadership and has become a top priority of the School of Science. The goals of the initiative 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 platform from which to address this global health imperative. The program would bring MIT's leading memory and neurobiology researchers together with researchers from other disciplines, including engineers, computer scientists, economists, urban planners, and social policy experts, including clinicians and industry partners, into a single cohesive group to think creatively about current and future needs and to collectively tackle ambitious ideas that would not otherwise be pursued. High-risk flagship projects, created across a diverse range of expertise, would include a whole-systems level perspective that would extend beyond the traditional clinical pathology and genetic approaches of today to include such vital aspects as understanding memory loss and developing "smart home" technologies for improved care. Frequent multidisciplinary discussion forums and seminars would enable the open sharing of data and accelerated development of ideas for growth into new areas.

The first five years of the Aging Brain Initiative would be devoted to a four-pronged approach that consists of research that could be implemented immediately to help us

understand both healthy and unhealthy brain aging and to develop real-world solutions that reduce cognitive decline, aid home care, and point toward a cure for conditions such as dementia. Specifically, the initiative plans to identify biomarkers of aging, develop circuit-specific therapeutics, personalize approaches to treatment, and uncover the secrets to healthy aging.

Faculty Research Summaries

Mark Bear

Mark Bear, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, is investigating how the brain is modified by experience, deprivation, and disease. His laboratory's overarching interest is in the question of how experience and deprivation modify synaptic connections in the brain. Experience-dependent synaptic plasticity is the physical substrate of memory. This plasticity 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 both vulnerable to numerous psychiatric and neurological diseases and contributes to their symptoms.

The 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 inputs to the visual cortex rapidly lose strength and, with a delay, the open-eye 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. We are currently applying the latest optogenetic and microendoscopic techniques to this problem. Further, insights into how synapses depress or potentiate have possible clinical applications for the treatment of amblyopia, and we are working with clinicians at Children's Hospital Boston to apply this knowledge.

The hippocampus is a cortical structure that is critical to various 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, we applied insights gained from a theoretical analysis of synaptic plasticity in the visual cortex 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 determine the molecular basis of bidirectional synaptic plasticity. The insights gained here can not only be applied to synaptic modifications elsewhere in the brain, but are also relevant to understanding hippocampus-dependent memory function and diseases of cognition.

In the course of studying LTD, we 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 the activation of metabotropic glutamate receptor 5 (mGluR5) and requires immediate translation of mRNAs at synapses. While studying this form of synaptic plasticity, we discovered that protein synthesis (and LTD) downstream of mGluR5 is exaggerated in the mouse model of fragile X syndrome. Human fragile X syndrome, caused by the silencing of the FMR1 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, contributing to many symptoms of the disease. Subsequent tests of this theory have shown that inhibition of mGluR5 can correct multiple mutant phenotypes in animal models of fragile X, ranging from the mouse to the fruit fly. 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 wherein genetic diseases of brain development, historically viewed as untreatable, may be ameliorated, or even corrected, with appropriate therapy.

Kwanghun Chung

Kwanghun Chung, Picower Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences, and Hemholtz Career Development Assistant Professor, Institute for Medical Engineering and Science, joined MIT in October 2013. He is also a principal investigator at the Picower Institute for Learning and Memory. His laboratory staff is an interdisciplinary research team that is devoted to developing and applying novel technologies for the integrative and comprehensive understanding of the brain. His group has continued to improve the CLARITY technology that transforms intact brains into transparent hybrids for holistic imaging and molecular phenotyping. Recent research advances by the group include active transport of charged molecules within or from charged matrix, an invention for which a patent application has been filed with the US Patent Office. A paper on a new transport mechanism is currently under review by a well-respected journal. Professor Chung was named a 2014 Searle Scholar, a 2015 NARSAR Young Investigator, and was selected as one of Cell's "40 Under 40" noteworthy young scientists. Since July 2014, Professor Chung has travelled extensively to speak about CLARITY imaging at various invited lectures, including at the Baylor College of Medicine, the Case Western Reserve School of Medicine, and Stanford University. He also taught a short course on the advancements in brain-scale and automated anatomical techniques for the Society for Neuroscience. Professor Chung taught HST.562 Imaging and Sample Processing and has been responsible for the IMES Distinguished Lecture Series. He also served on the IMES Committee on Academic Programs as well as the Graduate Admissions Committee at the Department of Chemical Engineering.

Myriam Heiman

Myriam Heiman is assistant professor of neuroscience, Department of Brain and Cognitive Sciences, and a core member of the Broad Institute. The focus of research in the Heiman group is to understand the basis of cell vulnerability or dysfunction in

neurodegenerative and psychiatric disease. We seek to understand what combinations of gene products lead to vulnerability to genetic or environmental insults in the case of neurodegenerative disease, as well as which cell types are most important in considering the actions of antipsychotic drugs. We combine genetic and biochemical methods to study gene expression profiles and vulnerability with neuronal cell-type specificity, as well as making use of the latest developments in genetic manipulation techniques and RNA sequencing. In the past year, we have reported the development of a new genetic screening methodology called synthetic lethal screening in the central nervous system, which has identified the age-regulated gene *Gpx6* as protective in Huntington's disease models. We have also identified the protein complex PRC2 as a master regulator of the transcriptional dysregulation that is associated with Huntington's disease. Because several PRC2 inhibitors have been developed as anti-cancer agents, it may be possible to target this complex as a treatment for Huntington's disease.

Troy Littleton

Troy Littleton is Picower Professor of Neuroscience, Departments of Biology and Brain and Cognitive Sciences. The focus of the Littleton laboratory's work is to understand how neuronal synapses form, function, and undergo plasticity. To complement these studies, we also study how alterations in neuronal signaling contribute to several brain diseases, including epilepsy, autism, and Huntington's disease. We 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 analysis and functional analysis have confirmed that key neuronal proteins and the mechanisms they govern are remarkably similar. Given this, we are attempting to elucidate the pathways mediating neuronal signaling using *Drosophila* as a model system. Recent progress in the laboratory includes new studies into how the calcium sensor synaptotagmin regulates synaptic vesicle fusion and the initiation of synaptic communication within the brain. Together with our clinical collaborators, we identified and characterized point mutants in synaptotagmin 2 that cause human lower motor neuron disease, the first demonstration of any clinical link to the synaptic vesicle fusion machine. We modeled these autosomal dominant point mutants in *Drosophila* and found that they perturb synaptic transmission by disrupting the function of a synaptotagmin multimer. We also examined how complexin functions as a fusion clamp, genetically testing several models for how the protein prevents the spontaneous release of vesicles. We also generated new transgenic tools that allow visualization of exocytotic events occurring through both spontaneous and evoked release at individual release sites, allowing the definition of general rules for vesicle fusion at single active zones for the first time in any system. We used this tool to characterize the relationship between spontaneous and evoked release, and examined how single-release-site probability and release mode are regulated at a glutamatergic synapse. We also examined how retrograde signaling modulates structural plasticity at synapses and characterized the molecular components that mediate this retrograde signaling pathway. By characterizing how neurons integrate synaptic signals and modulate synaptic growth and strength, we are bridging the gap between molecular components of the synapse and the physiological responses they mediate.

Earl Miller

Earl Miller is Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences. The overarching goal of Earl Miller's laboratory is to understand cognitive functions 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, allowing 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 technology with investigation of 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 learning. They found that when animals learn the categories of objects or when they learn that certain objects belong together, there are increases in brain wave synchrony between the prefrontal cortex (the brain's executive area) and brain areas involved in learning, the striatum and the hippocampus. This suggests that brain areas that "hum" together, learn together.

Elly Nedivi

Elly Nedivi is Picower Professor, 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), we focused on several and characterized their very different activities, showing that each provides unique insight into plasticity mechanisms.

Motivated by the large number of CPGs that affect neuronal structure, the Nedivi laboratory has been collaborating with Peter So's lab 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. We found unambiguous evidence of dendritic growth and retraction and of branch tip additions in the adult brain. Surprisingly, the data singled out gamma-aminobutyric-acid-ergic interneurons as those capable of structural dynamics, suggesting that circuit rearrangement is restricted by cell-type-specific rules. We have also developed methods for the labeling and chronic monitoring of excitatory and inhibitory synapses across entire neuronal arbors in the mouse visual cortex in vivo that provide the basis for a new research direction. This effort was recently funded by an NIH BRAIN award, where we proposed high-speed monitoring of sensory-driven synaptic activity across all inputs to single living neurons in the context of the intact cerebral cortex.

Mriganka Sur

Mriganka Sur is Paul E. Newton Professor of Neuroscience, Department of Brain and Cognitive Sciences, and Director of the Simon's Center for the Social Brain. Mriganka

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 2015 included three major findings.

Modulation of cortical processing by acetylcholine during attention and arousal powerfully influences information processing and brain states, causing robust desynchronization of local field potentials and strong decorrelation of responses between neurons. The Sur lab found that intracortical cholinergic inputs to mouse visual cortex specifically and differentially drive a defined cortical microcircuit: they facilitate somatostatin-expressing inhibitory neurons that in turn inhibit parvalbumin-expressing inhibitory neurons and pyramidal neurons. This inhibitory–disinhibitory circuit provides a mechanistic basis for temporal structure in cortical populations and demonstrates the crucial role of neuromodulatory drive in actively shaping the dynamics of neuronal activity.

Rett syndrome is a severe childhood-onset neurodevelopmental disorder caused by mutations in methyl-CpG-binding protein 2 (MECP2), with known disturbances in catecholamine synthesis. The Sur lab showed that treatment with a β 2-adrenergic receptor agonist increases survival, rescues abnormalities in respiratory function and social recognition, and improves motor coordination in male and female MECP2-mutant mice. The study revealed abnormalities in a microRNA-mediated pathway, downstream of brain-derived neurotrophic factor, that affects insulin-like growth factor 1 (IGF1) expression in MECP2 mutant mice, and showed that β 2-adrenergic agonists restored the observed molecular alterations. Finally, co-treatment with a β 2 agonist and recombinant human IGF1 resulted in powerful additive treatment effects. These data support a role for growth factor deficits as an underlying mechanism of Rett syndrome, and introduce β 2-adrenergic receptor agonists as potential therapeutic agents in combination with IGF1 for treatment of the disorder.

The Sur laboratory received BRAIN Initiative awards from NIH and NSF for developing cutting-edge two-photon technologies for massive-scale imaging of single-neuron activity. The laboratory is using such technologies to probe the function of cortical areas and circuits in the mouse brain involved in learning, memory, and perceptual decisions. These large-scale recordings have revealed surprising results: in short-term memory-guided visual decision tasks, crucial epochs of memory-related persistent activity appear in the motor cortex, where they are required for execution of the task.

Susumu Tonegawa

Susumu Tonegawa is Picower Professor of Neuroscience, Department of Biology and Department of Brain and Cognitive Sciences. Susumu 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:

- Competitive neural circuits controlling the emotional valence of contextual memories were found;

- Inability to recall memories formed in an amnesic state was found to be caused by a failure of access rather than a failure of consolidation; and
- Optogenetic activation of positive memories was shown to be sufficient to alleviate and reverse depression-related symptoms in mice.

Bidirectional Switch of the Valence Associated with a Hippocampal Contextual Memory Engram

The valence of memories is malleable because of their intrinsic reconstructive property. This property of memory has been used clinically to treat maladaptive behaviors. However, the neuronal mechanisms and brain circuits that enable the switching of the valence of memories remain largely unknown. We investigated these mechanisms by applying the recently developed memory engram cell manipulation technique. We labeled with channelrhodopsin-2 a population of cells in either the dorsal dentate gyrus (DG) of the hippocampus or the basolateral complex of the amygdala (BLA) that were specifically activated during contextual fear or reward conditioning. Both groups of fear-conditioned mice displayed aversive light-dependent responses in an optogenetic place avoidance test, whereas both DG- and BLA-labeled mice that underwent reward conditioning exhibited an appetitive response in an optogenetic place preference test. Next, in an attempt to reverse the valence of memory within a subject, mice whose DG or BLA engram had initially been labeled by contextual fear or reward conditioning were subjected to a second conditioning of the opposite valence while their original DG or BLA engram was reactivated by blue light. Subsequent optogenetic place avoidance and preference tests revealed that although the DG-engram group displayed a response indicating a switch of the memory valence, the BLA-engram group did not. This switch was also evident at the cellular level by a change in functional connectivity between DG engram-bearing cells and BLA engram-bearing cells. Thus, we found that in the DG, the neurons carrying the memory engram of a given neutral context have plasticity such that the valence of a conditioned response evoked by their reactivation can be reversed by reassociating this contextual memory engram with a new unconditioned stimulus of an opposite valence. Current work provides new insight into the functional neural circuits underlying the malleability of emotional memory.

Engram Cells Retain Memory Under Retrograde Amnesia

Memory consolidation is the process by which a newly formed and unstable memory transforms into a stable long-term memory. It is unknown whether the process of memory consolidation occurs exclusively through the stabilization of memory engrams. By using learning-dependent cell labeling, we identified an increase of synaptic strength and dendritic spine density in consolidated memory engram cells. Although these properties are lacking in engram cells under protein synthesis inhibitor-induced amnesia, direct optogenetic activation of these cells results in memory retrieval, and this correlates with retained engram cell-specific connectivity. We propose that a specific pattern of connectivity of engram cells may be crucial for memory information storage and that strengthened synapses in these cells critically contribute to the memory retrieval process.

Activating Positive Memory Engrams Suppresses Depression-like Behavior

Activating positive memory engrams suppresses depression-like behavior. Stress is considered a potent environmental risk factor for many behavioral abnormalities, including anxiety and mood disorders. Animal models can exhibit limited but quantifiable behavioral impairments resulting from chronic stress, including deficits in motivation, abnormal responses to behavioral challenges, and anhedonia. The hippocampus is thought to regulate the stress response negatively and to mediate various cognitive and mnemonic aspects of stress-induced impairments, although the neuronal underpinnings sufficient to support behavioral improvements are largely unknown. In this work we acutely rescued stress-induced depression-related behaviors in mice by optogenetically reactivating dentate gyrus cells that were previously active during a positive experience. A brain-wide histological investigation, coupled with pharmacological and projection-specific optogenetic blockade experiments, identified glutamatergic activity in the hippocampus–amygdala–nucleus accumbens pathway as a candidate circuit supporting the acute rescue. Finally, chronically reactivating hippocampal cells associated with a positive memory resulted in the rescue of stress-induced behavioral impairments and neurogenesis at time points beyond the light stimulation. Together, the data suggest that activating positive memories artificially is sufficient to suppress depression-like behaviors and point to dentate gyrus engram cells as potential therapeutic nodes for intervening with maladaptive behavioral states.

Li-Huei Tsai

Li-Huei Tsai is Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences. The Tsai laboratory uses multidisciplinary approaches to study neuropathologies that affect cognitive function. We focus on neurodegenerative disorders, such as Alzheimer’s disease (AD), and have an additional interest in neurodevelopmental disorders, such as autism and schizophrenia. In particular, we are interested in the epigenetic control of gene expression as it affects cognitive function in the brain. Epigenetic modifications include those that affect gene expression without altering DNA sequence. These mechanisms include the modification of histone proteins in the chromatin, via enzymes such as the histone deacetylases (HDACs), as well as DNA methylation and post-transcriptional control of gene expression by microRNAs. Our most recent work also suggests that the cleavage of the DNA itself, particularly via DNA double-strand breaks, may represent a novel form of epigenetic control of gene expression.

Previous work in our laboratory has shown the histone deacetylase 2 (HDAC2) enzyme to be a negative regulator of learning and memory genes that is upregulated following neurotoxicity and in AD. At the same time, we have shown that the activity of histone deacetylase 1 is neuroprotective against AD-like pathology. These studies have brought epigenetics-mediated gene expression to the forefront of memory research and ignited work to target epigenetic mechanisms for therapeutic intervention of memory disorders. Recently, the laboratory further identified the relationship of genome integrity and cognitive decline by showing the accumulation of DNA-damage in presymptomatic neurodegenerative mouse models and human patients’ brains, and also showing that this damage is likely caused by compromised DNA repair machinery. Unexpectedly, this work suggests that DNA double-strand breaks produced by topoisomerase 2b are,

in fact, necessary for early-response gene expression induced by neuronal activity. This work also establishes a new general mechanism for how activity regulates neuronal gene expression and explains why compromised DNA repair in neurons could lead to dysregulation of activity-regulated genes.

Although our early work showed that cyclin-dependent kinase 5 (Cdk5), in concert with its physiological activator p35, is crucial for brain development, generation of the p25 fragment, via calpain cleavage, has been associated with neurotoxicity and neurodegeneration. In a 2014 publication, we reported that this cleavage event is induced by neuronal activity and happens in a N-methyl-D-aspartate receptor and in a manner dependent on calcium/calmodulin-dependent protein kinase I. We created a calpain-resistant p35 mutant that is defective in p25 generation and generated a “knock-in” mouse model replacing the endogenous WT p35 gene. The p35 cleavage mutant mice are refractory to β -amyloid ($A\beta$) peptide-induced synaptic depression as well as to amyloid pathology and neuroinflammation in a mouse Alzheimer’s disease model. These results provide strong evidence supporting the notion that p25 generation and excessive Cdk5 activation are important mediators in $A\beta$ -induced synaptic deficits and neurodegeneration phenotypes. In line with this work, our recent study showed that chronic stress also leads to the upregulation of p25 generation, increased HDAC2, and reduced synaptophysin levels in the hippocampus. Using optogenetic and designer receptors exclusively activated by designer drugs techniques, we pinpointed a specific amygdala–hippocampus pathway that mediated these stress-induced deficits in cognitive function and cellular pathology. Chronic stress in the p35 cleavage mutant mice did not lead to p25 generation and pathology, indicating that p25 /Cdk5 activity in the hippocampus mediates chronic behavioral stress-induced hippocampal dysfunction.

In collaboration with Manolis Kellis of the Department of Electrical Engineering and Computer Science, we embarked on an in-depth bioinformatic examination of changing chromatin states in the hippocampus of the CK-p25 mouse model of AD at both early and later stages of induced neurodegeneration. This study represents a first attempt to investigate the chromatin state changes in the presymptomatic and symptomatic stage of AD-like neurodegeneration using the inducible CK-p25 mouse model, and to use the data to interpret human late-onset sporadic AD genetics on the basis of genome-wide association studies (GWAS). Expression analysis in CK-p25 hippocampus found that the expression of neuronal genes supporting synaptic function and cognition gradually declined, whereas the expression of innate immune response genes from microglia and monocytes markedly increased even in the presymptomatic stage. ChIP using multiple chromatin state markers in the CK-p25 hippocampus then revealed that human AD GWAS risk alleles, especially those in the non-coding regions, show enrichment in enhancers that are altered during AD-like neurodegeneration. Remarkably, AD risk alleles are significantly enriched in increased immune enhancers, but not enriched in decreased neuronal enhancers. These results suggest that genetic factors influence the increased immune response gene expression, whereas nongenetic factors may contribute to the decreased neuronal gene expression in AD.

In the realm of neurodevelopmental disorders that impact cognition, several recent studies from our laboratory, using both mouse models and human neurons, reveal

novel mechanisms for defects in neuronal maturation and function associated with autism- and schizophrenia-associated genetic variants. Siegert et al. found that disease-associated single-nucleotide polymorphisms (SNPs) in the MIR137 gene caused levels of the microRNA 137 (miR-137) to increase in human induced neurons derived from healthy individuals as well as from schizophrenia patients carrying the disease haplotype. This increase, in turn, leads to the downregulation of key presynaptic proteins, such as synaptotagmin 1, complexin 1, and N-ethylmaleimide-sensitive fusion protein. We then modeled this phenotype in mouse models, and showed that even a mild increase of miR-137 has deleterious consequences for presynaptic function, including altered presynaptic vesicle distribution, reduced synaptic vesicle release, and impaired synaptic plasticity. Down-regulation of miR-137 in induced neurons derived from human subjects carrying the disease haplotype restored the expression levels of presynaptic target genes, indicating a therapeutic potential for the downregulation of miR-137.

Another recent study from the lab used human induced neurons carrying a different schizophrenia GWAS SNP, in an intronic region of the human CACNA1C gene, which encodes an L-type calcium channel. After creating induced neurons from more than 20 human fibroblast lines, we determined that the presence of this SNP overall increases the expression of the CACNA1C channel, which results in increased L-type calcium channel current density. SNPs in the ANK3 gene, which encodes the ankyrin-G protein, have been associated with autism spectrum disorders and schizophrenia in GWAS. Using in utero electroporation combined with painstaking morphological analyses, Durak et al. found that ankyrin-G regulates canonical Wnt signaling by altering the subcellular localization and availability of β -catenin in proliferating cells. Ankyrin-G loss-of-function increases β -catenin levels in the nucleus, thereby promoting neural progenitor proliferation. These results suggest that ankyrin-G is required for proper brain development and provide a mechanism by which dysregulation of the ANK3 gene may contribute to neurodevelopmental phenotypes.

Kay Tye

Kay Tye is Picower Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences. Since Dr. Tye's arrival at the Picower Institute in January 2012, she has been working to use reverse translational approaches 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 of the laboratory is identifying 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. Some of the research from the Tye laboratory has been reported in two publications that describe the identification of a novel pathway from the amygdala to the ventral hippocampus that can bidirectionally control anxiety-related behaviors and social interaction, respectively. Furthermore, the laboratory has examined the functional encoding dynamics of optogenetically identified midbrain-projecting lateral hypothalamic neurons during a reward-seeking task, and shown that lateral hypothalamic projections to the ventral tegmental area control compulsive sucrose-

seeking behavior; this work was featured on the cover of *Cell*. The laboratory has also published a study, featured on the cover of *Nature*, that describes a circuit mechanism for differentiating positive and negative emotional associations. Together, we 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 Wilson is Sherman Fairchild Professor in Neurobiology, Department of Brain and Cognitive Sciences, and Department of Biology. Work in Matthew A. 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. Previous experiments 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 also demonstrated that 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. Professor Xu's laboratory studies how experience induces long-lasting changes in synaptic transmission (synaptic plasticity) important for information coding in the central nervous system. We use a combination of molecular, electrophysiological, and behavioral analyses in the rodent model system to study critical players in synaptic plasticity and learning and memory. The overarching goal is to understand the molecular mechanisms of neural plasticity that are essential for information processing and storage in the brain, and their dysfunction in diseases such as autism, schizophrenia, bipolar disorder, and mental retardation.

Signaling Scaffold for Synaptic Plasticity

In one line of research, we discovered that different scaffold proteins influence synapses differently in aspects including dependency on neuronal activity, receptor trafficking, and the kinetics of synaptic responses. These results suggest that scaffold proteins coordinate the structural and signaling interactions among receptors, chaperone proteins, and signaling cascades, and most likely control the proper signal transduction and biophysical properties at the synapses critical for learning and memory. As a proof of principle, we recently found that PSD-95, one prominent postsynaptic scaffold protein, is important for the durability of fear memory but not for the initial acquisition of the memory, suggesting the involvement of PSD-95 in specific phases of memory formation. This finding is strongly correlated with the synaptic function of PSD-95 in promoting and stabilizing functional connections during development and learning. We

are now mapping the landscape of synaptic diversity and signaling specificity controlled by scaffold proteins. Using comprehensive proteomic analysis focused on synapses, we hope to begin to understand the molecular logics behind the synaptic computation. Additional studies in the laboratory have characterized the role of Shank family proteins, associated with autism spectrum disorders and schizophrenia, in synaptic transmission and receptor functions.

Regulation of Calcium Homeostasis in Learning and Memory

Calcium is the essential secondary messenger in the brain, translating extracellular events into intracellular signaling cascades important for activity-dependent neural plasticity via processes dependent on the calcium-binding protein, calmodulin (CaM). Dysregulation of calcium homeostasis is thought to contribute to neuropsychiatric diseases, such as schizophrenia, and to normal aging. Researchers focused on a CaM-binding protein, neurogranin, because it is centrally localized in principal neurons throughout the cortex and hippocampus, at the subcellular region where calcium signaling is essential for synaptic plasticity, and has been associated with neurological and neuropsychiatric disorders, including mental retardation and schizophrenia. We found that in the hippocampus, experience-dependent translation of neurogranin is a gate for contextual memory formation through controlling the threshold of long-term synaptic plasticity. We are currently investigating both the cellular mechanisms underlying the role of neurogranin in synaptic plasticity and the molecular mechanisms underlying the experience-dependent translation of neurogranin. We have also studied the role of neurogranin in the visual cortex, given the strong implication of its involvement in experience-dependent plasticity, and in the potential dysfunction of cortical plasticity in schizophrenia. We found that the level of neurogranin dictates the experience-dependent stabilization of excitatory synapses in the primary visual cortex. Decreased neurogranin levels led to a profound loss of excitatory synaptic transmission on normal visual experience through a lowered threshold for long-term depression of excitatory synaptic transmission. We are currently investigating the functional consequences of this profound alternation of cortical plasticity in visual processing and visual cortex development. Our results are beginning to elucidate a critical mechanism for regulation of the calcium signaling that is important for learning and memory.

Li-Huei Tsai

Director

Picower Professor of Neuroscience