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

Awards and Honors

Emery Brown was elected Fellow of the National Academy of Inventors and Fellow of the Institute of Mathematical Statistics, and received the Excellence in Research Award from the American Society of Anesthesiologists.

Kwanghun Chung received the McKnight Technological Innovations in Neuroscience Award and the Packard Fellowship for Science and Engineering.

Myriam Heiman received the Fay/Frank Award from the Brain Research Foundation, the Jeptha H. and Emily V. Wade Award from MIT, and was named to the Latham Career Development Chair at MIT.

Earl Miller was elected to the Memory Disorders Research Society, received the Kent State University Professional Achievement Award, and was the 2016 commencement speaker at Kent State University.

Li-Huei Tsai received the Javits Neuroscience Investigator Award, which is administered by the National Institute of Neurological Disorders and Stroke.

Kay Tye received the Presidential Early Career Award, the Freedman Award, and the Harold E. Edgerton Faculty Achievement Award.

Rose Faghih (postdoctoral associate, Brown Laboratory) was named a DiscoverE Today New Faces of Engineering honoree.

Lea Hachigan (graduate student, Heiman Laboratory) received the Walle J.H. Nauta Award for Excellence in Graduate Teaching.

Hannah Iaccarino (graduate student, Tsai Laboratory) received the Department of Brain and Cognitive Sciences (BCS) travel award.

Hiruy Meharena (postdoctoral associate, Tsai Laboratory) was given the Burroughs Wellcome Fund Postdoctoral Enrichment Program Award.

Rebecca D. Shi (graduate student, Xu Laboratory) received the BCS Hans Lucas Teuber Award for Outstanding Academics.

Martine Therrien (postdoctoral associate, Myriam Heiman, Broad Institute) received a Fonds de Recherche du Québec-Santé postdoctoral fellowship.

The Walle J.H. Nauta Award for Outstanding Research was given to Francisco X. Peña and Rebecca D. Shi (graduate students in the Xu laboratory) and to Elizabeth De Laittre (graduate student in the Bear laboratory).

The 2016 Infinite Mile and Kilometer Award winners were Asha Bhakar (director of development), Takashi Kitamura (Tonegawa laboratory), Ram Madabhushi (Tsai laboratory), and Michele Pignatelli di Spinazzola (Tonegawa laboratory).

Research Breakthroughs

Major research advances in Picower Institute faculty laboratories during academic year 2016 are summarized below.

Researchers in the 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 for how this recovery occurs, 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 b-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.

The Bear laboratory has examined the role that parvalbumin-expressing (PV+) inhibitory neurons play in two forms of experience-dependent synaptic strengthening in the primary visual cortex of adult mice. They found that PV+ inhibitory neurons were critical in the expression of response strengthening resulting from enriched visual experience (termed stimulus-selective response potentiation) and its behavioral correlate, familiarity recognition. In contrast, PV+ inhibitory neurons did not play a role in the synaptic strengthening associated with adult ocular dominance plasticity resulting from a prior period of monocular deprivation.

The Chung laboratory has developed several new technologies. One new technology, termed stochastic electrotransport, enables 30-fold to 50-fold faster labeling of the target molecules and structures in the brain. This method will accelerate the pace of brain mapping and phenotyping of animal disease models and human clinical samples. Another new technology, termed SWITCH, enables high-dimensional proteomic

imaging of complex biological systems. This technique will allow researchers to study complex interactions among multiple pathogenic factors and various cell types.

The Chung laboratory has also developed a new technology, termed MAP, that enables super-resolution proteomic imaging of the brain. This method will allow researchers to extract subcellular details, permitting clear molecular identification of cells as well as their brain-wide intercellular connectivity. The Chung laboratory will use these technologies to establish a comprehensive high-resolution map of the normal brain as well as to map diseased brains.

Heiman laboratory researchers revealed that a gene called Foxp2 is involved in the pathophysiology of Huntington's disease. By altering the levels of this gene, researchers can rescue the behavioral phenotypes seen in mouse models of the disease. The Heiman laboratory also has applied a new method, called sequence and ligation independent cloning, to identify genes that enhance the toxicity of the mutant huntingtin gene, performing the first-ever genome-wide genetic screen in the mammalian nervous system.

The Littleton laboratory discovered that the SHANK autism gene regulates synaptic Wingless/Wnt signaling, and that a conserved vesicular trafficking pathway regulates retrograde signaling at synapses.

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. In fact, this is arguably the most-studied neural correlate of a cognitive function. This year, the Miller laboratory published a study that has upended this notion. All previous studies have used averages across multiple instances (trials), with the idea that averaging simply improves the signal-to-noise ratio. The problem is that the brain does not 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.

Even though 60,000 people a year in the US alone undergo general anesthesia, no one knows why it renders a person 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 an animal can be awakened from general anesthesia via deep brain stimulation. Preliminary data suggests that this is possible.

The Miller laboratory has just published a new theoretical paper that aims to overturn more dogma. It has been assumed since the early days of modern neuroscience that every neuron has one function. Researchers in the Miller laboratory have shown, via computational modeling, that many cortical neurons must be multifunctional. Without that, the brain lacks the horsepower for complex thought. It turns out that this fits well with recent observations in experiments designed to test this hypothesis.

Synaptic remodeling observed in vivo is commonly thought to represent rearrangements in microcircuit connectivity. The Nedivi laboratory has recently observed a new, reversible type of synapse dynamics, unique to inhibitory synapses, that could provide flexible, input-specific gating of stable excitatory connections.

Researchers in the Nedivi Laboratory have also identified a new component of the endocytic complex, EndoB2, that partners with the activity-regulated synaptic protein CPG2 to facilitate activity-dependent glutamate receptor endocytosis, a key aspect of synaptic plasticity. More, Nedivi Laboratory scientists have characterized the region of the human SYNE1 gene that is homologous to rat CPG2, and have shown that it encodes a protein that is localized to synapses and is functionally interchangeable with rat CPG2. This suggests that human SYNE1, a risk gene for bipolar disorder, plays a role in regulating glutamatergic synaptic function.

Researchers in Mriganka Sur's laboratory have shown that neurons in the visual cortex have reliable responses to natural scenes, allowing these scenes to be processed rapidly. Response reliability is driven in part by spatial correlations within the stimulus—neurons fire more reliably when activated together with specific ensembles of partner cells. The Sur laboratory also dissected the roles of visual, posterior parietal, and frontal motor cortex in the perception and performance of visually driven tasks, using optogenetic inactivation to reveal the roles of the three areas in encoding stimulus, choice, and behavior through the course of the task.

Using optogenetic technology to label and manipulate memory engram cells, Tonegawa laboratory researchers further elucidated the role of ocean and island cells in temporal and contextual memory, and the neural circuits controlling contextual and temporal fear memory. The Tonegawa laboratory also made use of Ca2+ imaging to discover that grid cells exist in island and ocean cell populations in similar proportions, but that grid cells found in island populations are significantly more speed modulated. This discovery was published shortly before a similar discovery announced by the Nobel Prize–winning Moser group.

The Tonegawa laboratory made a landmark discovery that overturns previously assumed knowledge about Alzheimer's disease and the state of memories in early Alzheimer's disease. Tonegawa researchers used optogenetic and memory engram manipulation technology and showed that memories remain intact even in early stages of Alzheimer's disease, meaning that memory failure is because of retrieval failure rather than storage failure. In addition, they enacted a protocol of long-term potentiation that strengthened engram cells' dendrites; this holds promise as a method for the restoration of memories "lost" to Alzheimer's disease.

In collaboration with Kwanghun Chung [Chemical Engineering, BCS, Institute for Medical Engineering and Sciences (IMES), Picower Institute], the Tsai laboratory produced the first four-dimensional map of amyloid pathology in a mouse model of Alzheimer's disease.

In collaboration with Ed Boyden (Media Lab, BCS, McGovern Institute for Brain Research, Picower Institute) and Emery Brown (BCS, IMES, Picower Institute), the Tsai laboratory demonstrated the possibility of clearing pathology related to Alzheimer's disease by sensory stimulation of the brain in several different mouse models.

The Tsai laboratory continues to decipher the roles of Class I histone deacetylases in regulating brain development and cognitive function. Researchers found that histone deacetylase 3 (HDAC3) regulates social behavior and cognitive function via interactions with the proteins MeCP2 and FoxO.

A new study from Kay Tye's laboratory has identified 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.

Spatial learning requires the hippocampus, and the replay of spatial sequences during hippocampal sharp wave-ripple events of quiet wakefulness and sleep is believed to play a crucial role. The Wilson laboratory found that neurons that signal reward in an area of the brain known as the ventral tegmental area coordinated with hippocampal sharp wave-ripple events that replayed recent experience during quiet wakefulness ("thinking"), but not during sleep ("dreaming"), suggesting different roles for memory processing during these states.

The Xu laboratory found that experience-dependent equilibration of excitatory synaptic transmission in the primary visual cortex during development is critical for establishing visual perception. The Xu laboratory also found that changes in neurogranin (a calmoulin-binding protein) levels lead to shifts in the phosphoproteome. Such changes can also affect long-term potentiation of synaptic transmission by regulating PP2B activity.

Personnel

In addition to 14 faculty members, the Picower Institute comprises other researchers, students, technical, and administrative support personnel. More than 300 community members participated in Picower Institute activities during academic year 2016: 14 faculty members, four visiting scientists and scholars, 67 postdoctoral associates, 93 undergraduate students, 32 graduate students, 73 research and technical staff, and 18 administrative and service staff.

Items of note during the academic year include the following:

- Dr. Steven Flavell was hired as a new Picower assistant professor of neuroscience, Department of Brain and Cognitive Sciences, beginning January 2016.

- Dr. Emery Brown, Edward Hood Taplin Professor of Medical Engineering and of Computational Neuroscience, joined the Picower Institute in October 2015.
- Erin Edwards was hired as the assistant director for administration in November 2015, replacing David Vaughn.
- Lauren Miller was hired as the Human Resources business partner in December 2015, replacing Ngoc Tran.
- Patrick Curtis was hired as a senior administrative assistant to Dr. Tsai in January 2016, replacing Constantine Zahariadis.
- Tracy Nash was hired as financial assistant in January 2016, replacing Silvia Darosa.
- Amanda Deveau was hired as an administrative assistant to Dr. Tye and Dr. Flavell in March 2016.
- Nina Palisano was hired as an administrative assistant to Dr. Bear in March 2016, replacing Suzanne Meagher.
- Brittany Greenough was hired as an office and administrative assistant for Picower Institute headquarters in June 2016, replacing Jiyoung Won.
- Casey Reisner was hired as an events and communications assistant in June 2016, replacing Najat Kessler.
- Dr. Asha Bhakar was promoted to director of development in May 2016.
- Dr. Joshua Sarinana is in transition from program administrator and science writer to the new communications administrator and science writer role.

Resource Development

The Picower Institute has enjoyed impressive success over recent years and that trend continued in AY2016. 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 Institute resource development efforts identified more than 109 collaborative funding opportunities; development staff worked closely with Picower Institute faculty to draft 18 prize nominations and 12 new philanthropic proposals. New philanthropic gifts and pledges to Picower Institute faculty for fiscal year 2016 totaled more than $5 million.

Because of the generous support provided from the JPB Foundation and the late Jeffry Picower, researchers at the Picower Institute have been able to continue their ambitious research efforts, venturing into groundbreaking and transformational areas of neuroscience that will lead to new and effective cures for brain illnesses. Two new gift commitments, totaling $800,000, to the Picower Institute Innovation Fund have allowed the continued support of this flagship high-risk innovation program. The commitments also permitted the expansion of this program to include two new members, Dr. Emery Brown and Dr. Steve Flavell, who are invaluable additions to the Picower Institute. In FY2016, the Picower Institute Innovation Fund and Junior Faculty Development Program allowed the Picower Institute to support breakthroughs that will permit better

mapping of the brain in three dimensions, better understanding of how synapses encode the information we've learned, and identification of brain circuits and disruptions that are key to various mental illnesses. Investing in this basic research has the potential to save lives and to result in direct and indirect economic effects.

Other notable new commitments include a generous $1 million gift from MIT Corporation member Jeffrey S. Halis '76 and his wife, Nancy. The gift will seed the first year of brain-aging projects at eight laboratories across MIT that are associated with the Aging Brain Initiative. The Robert A. and Renee E. Belfer Family Foundation also committed an additional $3.5 million to the Neurodegeneration Consortium, a collaborative enterprise comprising renowned scientists from MIT, the University of Texas MD Anderson Cancer Center, and Baylor College of Medicine. This new funding enables investigation of new ways to slow, stop, or reverse the progression of Alzheimer's and other neurodegenerative diseases and expands MIT's participation in the consortium. The Cure Alzheimer's Foundation also approved a $500,000 gift to MIT over the course of two years in support of Li-Huei Tsai and her research on Alzheimer's disease. More, MIT alumna Song-Yee Yoon gave a $1.6 million gift to support Kwanghun Chung's brain mapping efforts.

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 Director Li-Huei Tsai, along with eight founding faculty members from different disciplines; it has gained senior leadership support, including becoming a top priority of the School of Science. On April 19, 2016, MIT Chairman Robert Millard and his wife Bethany hosted an "Inside the Aging Brain Initiative" dinner to bring attention to the initiative. This dinner not only raised awareness for those invited, but also achieved far-reaching visibility among people interested in both learning more about the initiative and in supporting it.

The Picower Institute also hosted the biannual spring symposium, New Insights on Early Life Stress and Mental Health, in honor of its guest and generous donor, Ms. Barbara Picower. The event, which took place on May 12, provided informative conversation on the varied approaches taken and progress made for interventions to improve early life health. The event was exceptionally well attended (there were approximately 500 registrants) and resulted in many connections with potential donors and in increased visibility of the Picower Institute. The day concluded with an intimate dinner hosted by the Picower Institute and held at the Samberg Conference Center in the Morris and Sophie Chang Building at MIT.

Additionally, many smaller gifts from dedicated donors have proven vital to the Picower Institute's mission of advancing brain research. New funds included a $50,000 gift in support of Myriam Heiman's schizophrenia work from MIT alumnus Eduardo Elejalde.

Media Recognition

In academic year 2016, Picower Institute faculty published 24 articles in hallmark science journals (Science, Neuron, Cell, Nature, Nature Neuroscience, eLife, and Proceedings of the National Academy of Sciences), and in 92 peer-reviewed publications overall.

The Picower Institute issued 18 press releases in academic year 2016. Articles appeared in major media outlets, such as WBUR, ABC News, CBS News, the Today Show, Independent Television News (ITN), Fox News, the Washington Post, the Economist, Scientific American, Discover, the Huffington Post, the Telegraph, the Guardian, Wired, Science Daily, CNET, and MIT's Tech.

Programs and Activities

The Picower Institute was founded with the premise that collaboration among disciplines would be 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 holding a number of 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 that research advances about learning and memory mechanisms in the brain offer to science and society. Ongoing programs and activities are described below.

The annual Picower Lecture was named to honor and recognize the generous support of the Picower Foundation for neuroscience research at MIT. Each lecture features the work of a current leader in the area of brain research. This year's lecturer was Dr. Edvard Moser, a Nobel laureate and professor of neuroscience and director of the Kavli Institute for Systems Neuroscience at the Norwegian University of Science and Technology in Trondheim. His talk, "Grid Cells and the Cortical Representation of Space," took place on February 24, 2016.

The Picower Institute Colloquia series brings the highest caliber of learning and memory researchers 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, the colloquia speakers were Dr. Alcino Silva of the University of California at Los Angeles, Dr. Sheena Josselyn of the University of Toronto, Dr. John Flanagan of Harvard University, and Dr. Suzanne Zukin of Albert Einstein College of Medicine.

In the language of neuroscience, "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 to make improvements, in partnership with the administration, for the postdoctoral community. Throughout the past year, the association 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 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 second annual Brain and Cognitive Sciences community retreat was held on June 6 and 7, 2016. More than 140 Picower Institute members attended the event, which was held in Newport, RI, at the Marriott Hotel. The retreat was co-hosted by the department of Brain and Cognitive Sciences and the McGovern Institute. The retreat included nine speakers, of whom three were from the Picower Institute, and 14 posters from Picower Institute laboratories.

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. Aging Brain speakers were Dr. Philip De Jager of Harvard Medical School, Dr. Morgan Sheng of Genentech, and Dr. David Bennett of Rush University Medical Center.

Research programs enabled by philanthropic support from the JPB Foundation and the RIKEN Institute afford the Picower Institute a truly unique research environment, with support for faculty, laboratory members, and the administrative team. The programs include the MIT–Massachusetts General Hospital Clinical Fellowship Program, the Picower Neurological Disorder Research Fund, the Junior Faculty Development Program, the Symposium Fund, the Picower Institute Innovation Fund, and the RIKEN-MIT Center for Neural Circuit Genetics.

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 MIT, the center seeks to fully understand the brain mechanisms underlying specific cognitive phenomena such as memory or emotion. The RIKEN-MIT 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. By combining cutting-edge transgenic and viral vector techniques, in vivo multi-electrode recording technology, optical and magnetic imaging techniques, and behavioral studies, the RIKEN-MIT Center uses an interdisciplinary approach. The agreement between

MIT and the RIKEN Brain Science Institute funds the activities of the center, which principally supports the laboratory of Susumu Tonegawa.

Viral Gene Transfer Core

The Viral Gene Transfer Core was launched in the fall of 2008 by the Picower Institute in partnership with the McGovern Institute for Brain Research and the support of an anonymous donor. Dr. Rachael Neve, an internationally renowned expert in viral vector research, with more than 400 publications, assumed the directorship. A self-supporting service facility, the Viral Gene Transfer Core is a unique resource for MIT's neuroscience community that also serves external academic researchers. Viral gene delivery is a powerful adjunct to transgenic mice for sophisticated manipulations of neuronal function. The Viral Gene Transfer 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 will provide the basis for new treatments of neurological and psychiatric disorders.

iPS Core Facility

The iPS Core Facility, which was launched in November 2010 by the Picower Institute, integrates the various research goals of members of the Picower Institute, the McGovern Institute, and BCS 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, results in accelerated progress in this novel, dynamic, and competitive field. In fiscal year 2014, 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.

Currently, the iPS Core Facility has produced more than 60 patient-specific induced pluripotent stem (iPS) cells from schizophrenia, bipolar disease, depression, Rett syndrome, Alzheimer's disease, and Down syndrome, and also 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 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. Moreover, collaborations with researchers outside MIT have been continuing, with noteworthy interactions with the Broad Institute and the biotech industry. Many prominent articles that were based on data obtained while using the iPSC facility have been published and accepted in various journals, including Nature Neuroscience, PLoS One, and Molecular Psychiatry.

MIT researchers have leveraged the iPS facility's capabilities to receive external funding on numerous occasions. [Alzheimer's Disease Risk Genes in Human Microglia and Neurons Derived from iPSCs.] [Chemical Genomic Approaches to Neurobiology of DISC1.] [Takeda] [Belfer] [JPB Foundation, PIIF IV Research -TSAI FUND] [NIH The cdk5/p35 kinase] [Alana Foundation, Alana USA Fnd. Down Syndrome Research Fund]

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 Picower Institute investigators for studying neurological diseases. The facility has been constructed to utilize high-performance computing clusters for high-throughput quantitative data analysis, with particular focus on genomic and epigenomic data analysis. Since April 2015, the facility has provided workshops to the entire BCS community, hosted by Picower Institute bioinformatician Dr. Fan Gao, that are tailored to teaching the basics on use and applicability of current genomics and epigenomics software to graduate students and postdoctoral associates. 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 for participants to learn 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 CLARITY imaging core equipment facility was created to allow the Picower Institute to lead in using 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 provided by Picower Institute Assistant Professor Kwanghun Chung. The equipment includes a high-content rapid throughput imaging microscope system from Leica Microsystems and Leica's supporting software. The facility has been used heavily, particularly by the Chung, Sur, Tsai, and Tye laboratories; however, the equipment is available to all Picower Institute laboratories and is available for use 24 hours a day, 7 days a week. Videos and data collected using this new technology are shown at gatherings such as Brain Lunch, Plastic Lunch, and the winter brain conference; they will also be shared at upcoming Gordon Conferences. Most notable are videos, depicting clarified mouse and human post-mortem brains, that reveal new pathological information about 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 Institute 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. This initiative is led by Picower Institute Director Li-Huei Tsai, along with eight other founding faculty members from different disciplines; it has gained senior leadership support, becoming a top priority of the School of Science. The 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 would bring MIT's leading memory and neurobiology researchers together with members 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 needs of aging brains 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 extending beyond the traditional clinical pathology and genetic approaches of today, to include such vital aspects of the challenge as understanding memory loss and developing smart home technologies for improved care. Frequent multidisciplinary discussion forums and seminars would enable open sharing of data and accelerated pollination of ideas for growth into new areas.

The first five years of the Aging Brain Initiative are to be devoted to a four-pronged approach that consists of project- and team-based, immediately implementable research to help us understand both healthy and unhealthy brain aging, and to develop real-world solutions that reduce cognitive decline, support care at home, and point toward a cure for conditions such as dementia. Specifically, there are plans to identify aging biomarkers, develop circuit-specific therapeutics, personalize approaches to treatment, and uncover the secrets to healthy aging.

Faculty Research Summaries

Picower Institute faculty research areas are summarized below.

Mark Bear

Mark Bear is a professor of neuroscience in the Department of Brain and Cognitive Sciences. The overarching interest in Mark Bear's laboratory is in how the brain is modified by experience, deprivation, and disease—that is, how experience and deprivation modify synaptic connections in the brain. Experience-dependent synaptic plasticity is the physical substrate of memory. This plasticity also 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 vulnerable in numerous psychiatric and neurological diseases and 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 inputs to the visual cortex rapidly lose strength; 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's population. Thus, the visual cortex is an excellent preparation to connect the elementary molecular mechanisms of synaptic plasticity to their behavioral consequences. Researchers in the Bear laboratory 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; researchers 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 to conduct in other parts of the brain. In the early 1990s, researchers in the Bear group 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 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, 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 mGluR5 and requires immediate translation of mRNAs at synapses. While studying this form of synaptic plasticity, researchers discovered that protein synthesis (and LTD) downstream of mGluR5 is exaggerated in the mouse model of fragile X (FX). Human FX, which is 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 mouse models to fruit fly models. Human clinical trials were initiated based on the strength of this science, and results to date indicate that treatments can be developed to substantially benefit this patient population. 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.

Emery Brown

Emery Brown is the Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience in the Institute for Medical Engineering and Sciences and the Department of Brain and Cognitive Sciences. The Brown laboratory published two papers giving detailed characterizations of the neurophysiological (electroencephalogram) signatures of two widely used anesthetic drugs: sevoflurane and ketamine.

Sevoflurane is a modern ether anesthetic. Characterizing the signatures of sevoflurane is especially significant because they offer, for the first time, insight into the specific neural circuit mechanisms of how ether anesthetics act in the brain to produce states of unconsciousness. Sevoflurane produces highly structured alpha (8 to 12 Hz) and slow

(0.1 to 1 Hz) oscillations that have also been seen in propofol—another anesthetic that works by acting enhancing inhibition mediated by gamma-aminobutyric acid (GABA)—to disrupt normal information transmission among brain regions. This work makes explicit what is likely to be the primary neural circuit mechanism of ether, the first recognized anesthetic drug.

In contrast, unconsciousness induced by ketamine, which acts by blocking N-methyl-D-aspartate receptors, produces large-amplitude, slow-delta (0.1 to 4 Hz) oscillations that alternate with gamma (~ 27 to 40 Hz) oscillations. This unique pattern of oscillations suggests specific cortical, thalamic, and brainstem mechanisms for ketamine's actions.

Kwanghun Chung

Kwanghun Chung is the Hermann L. F. von Helmholtz Career Development Professor of Neuroscience in the Department of Brain and Cognitive Sciences, assistant professor in the Departmentsof Chemical Engineering, and core faculty in the Institute for Medical Engineering and Science. His laboratory staff is an interdisciplinary research team that is devoted to developing and applying novel technologies for integrative and comprehensive understanding of the brain. His group has continued to develop enabling technologies to accelerate the pace of scientific discovery and the development of therapeutic strategies in a broad range of biomedical research. Recent research advances by his group include tissue-processing technologies that are up to 50-fold faster than the conventional proteomic imaging of human brain tissues, and super-resolution and scalable proteomic imaging of large samples. Chung was named a 2015 Packard Fellowship for Science and Engineering Awardee and a 2016 McKnight Technological Innovations in Neuroscience Awardee. Since July 2015, Professor Chung has traveled extensively, including to Weizmann Institute, Temple University, and the Experimental Biology Annual Conference, to speak about the new technologies. Professor Chung taught HST.562 Imaging and Sample Processing and 10.032 Transport Phenomena. He also served on the IMES Committee for Academic Programs.

Steven Flavell

Steven Flavell is an assistant professor in the 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 (sleep, waking) and complex internal states (emotions)—are thought to be controlled by biogenic amine and neuropeptide neuromodulators. However, our understanding of the basic neural mechanisms that underlie behavioral state initiation, maintenance, and termination is still poor. 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 the Flavell laboratory is to understand how neural circuits generate sustained behavioral states and how physiological and environmental information is integrated into these circuits.

Dr. Flavell's recent studies have identified a neuromodulatory circuit that generates two opposing behavioral states in C. elegans. He used quantitative behavioral analyses

paired with genetics to show that serotonin and the neuropeptide pigment dispersing factor each acts 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 (GCaMP) 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. Dr. Flavell is now using his knowledge of this circuit to ask fundamental questions about how behavioral states are generated and how environmental cues influence state generation, including the following:

- What circuit-wide patterns of activity define the stable configurations for each behavioral state? How are these patterns stabilized by neuromodulators like serotonin? Toward this end, the laboratory is currently constructing a microscope that will be suitable for whole-brain calcium imaging.
- How does this circuit detect the feeding or satiety status of the animal, only generating roaming or dwelling states 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 in the process of characterizing these channels.
- How do animals compare current food levels with those of the recent past and adjust behavior accordingly? The Flavell laboratory is taking advantage of new cell-specific transcriptomics methods that they developed to examine how changes in gene expression might underlie these experience-dependent effects.

Myriam Heiman

Myriam Heiman is an assistant professor of neuroscience in the Department of Brain and Cognitive Sciences, and is a core member at the Broad Institute. The focus of research in the Heiman group is to understand the basis of cell vulnerability and dysfunction in neurodegenerative and psychiatric disease. Researchers seek to understand what combination of gene products leads to vulnerability in aging and neurodegenerative diseases of the basal ganglia, as well as which cell types are most important in considering the actions of antipsychotic drugs. Studies in the Heiman laboratory combine genetic and biochemical methods to perform cell-type-specific molecular and cellular studies in the mammalian nervous system. In the past year, the Heiman laboratory has optimized parameters for genetic screening in the brain and performed the first-ever genome-wide genetic screen in the mammalian nervous system, identifying genes that enhance or suppress mutant huntingtin toxicity. Researchers have also identified Foxp2 as a striatal neuron vulnerability factor in Huntington's disease and shown that restoring soluble Foxp2 levels can rescue behavioral deficits in two mouse models of Huntington's disease; performed cell type-specific translatome profiling to understand the cell type-specific effects of antipsychotic drug action; and, in collaboration with the Burge group in the Department of Biology, shown that subtypes of aged striatal medium spiny neurons show enhanced oxidative stress and dramatic changes in how mRNAs are translated.

Troy Littleton

Troy Littleton is a professor in the 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, researchers 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 analysis has confirmed that key neuronal proteins and the mechanisms they govern are remarkably similar. As such, the Littleton laboratory is attempting to elucidate the pathways mediating neuronal signaling using Drosophila as a model system. Recent progress in the laboratory includes new studies in how the postsynaptic compartment regulates neuronal development and signaling. Haploinsufficiency for SHANK3 is one of the most prevalent monogenic causes of autism spectrum disorders, making it imperative to understand how the SHANK family regulates neurodevelopment and synapse function. Researchers in the Littleton laboratory created the first animal model lacking all SHANK proteins and used the Drosophila neuromuscular junction, a model glutamatergic synapse, to characterize the role of SHANK at synapses. They also identified a novel function of SHANK in synapse size and maturity via regulation of Wnt signaling in the postsynaptic cell, and made important progress on characterizing how postsynaptic cells communicate with their presynaptic partners to induce synaptic plasticity through the release of activity-dependent retrograde signals. Laboratory staff had previously identified a Ca2+-dependent retrograde signaling pathway mediated by postsynaptic synaptotagmin 4 (Syt4). To identify proteins involved in postsynaptic exocytosis, researchers conducted a screen for candidates that disrupted trafficking of a pHluorin-tagged Syt4 at Drosophila neuromuscular junctions and characterized one candidate, the postsynaptic t-SNARE Syntaxin 4 (Syx4). Analysis of Syx4 mutants reveals that Syx4 mediates retrograde signaling, modulating the membrane levels of Syt4 and the transsynaptic adhesion protein neuroligin (DNlg1). Genetic interaction experiments demonstrate Syx4, Syt4, and dNlg1 regulate synaptic growth and plasticity. The findings suggested that a conserved postsynaptic SNARE machinery controls multiple aspects of retrograde signaling and cargo trafficking within the postsynaptic compartment. By characterizing how neurons integrate synaptic signals and modulate synaptic growth and strength, the Littleton laboratory is bridging the gap between molecular components of the synapse and the physiological responses they mediate.

Earl Miller

Earl Miller is the Picower Professor of Neuroscience in the Department of Brain and Cognitive Sciences. The overarching goal of his 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, which 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. Researchers found that when animals learn new categories, there are increases in brain wave synchrony between cortical areas. They 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 a professor in the 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 focused on several and characterized their very different activities, showing that each gene offers unique insight into diverse aspects of plasticity mechanisms.

Motivated by the large number of CPGs that affect neuronal structure, the Nedivi laboratory has been collaborating with Peter So's laboratory in the Department of Mechanical Engineering to develop multi-photon microscopy for large-volume, high-resolution imaging of dendritic arbor and synaptic structural dynamics in vivo. Researchers showed unambiguous evidence of dendritic growth and retraction and of branch tip additions in the adult brain. Surprisingly, the data singled out GABAergic interneurons as those capable of structural dynamics, suggesting that circuit rearrangement is restricted by cell type-specific rules. The Nedivi laboratory has also developed methods for labeling and chronic monitoring of excitatory and inhibitory synapses across entire neuronal arbors in the mouse visual cortex in vivo; this work is the basis for a new research direction, recently funded by an NIH BRAIN award, in which researchers 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 the Paul E. (1965) and Lilah Newton Professor of Neuroscience in the Department of Brain and Cognitive Sciences, and the Director of the Simons Center for the Social Brain. His 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 FY2016 included three major findings.

Intrinsic neuronal variability significantly limits information encoding in the primary visual cortex (V1). Certain stimuli can suppress this intertrial variability to increase the reliability of neuronal responses. In particular, responses to natural scenes, which have broadband spatiotemporal statistics, are more reliable than responses to stimuli such as gratings. Researchers sought to elucidate the role that spatial correlations in natural

scenes play in reliable coding and found that responses in mouse V1 were much less reliable, at both the single neuron and population level, when driven by images lacking spatial correlation. This change in reliability was because of a reorganization of between-neuron correlations. Strongly correlated neurons formed ensembles that reliably and accurately encoded visual stimuli; reducing spatial correlations in the stimulus reduced the activation of these ensembles, leading to an unreliable neural spiking code. Together with an ensemble-specific normalization model, these results suggest that the coordinated activation of specific subsets of neurons underlies the reliable coding of natural scenes.

The posterior parietal cortex (PPC) has been implicated in perceptual decisions, but its specific role at the interface between sensation and action remains unresolved. Researchers investigated the role of PPC in flexible sensorimotor transformations by training mice on a visual discrimination task. Optogenetic inactivation experiments revealed that both V1 and PPC were necessary during the stimulus period, but not during the motor response. Using two-photon calcium imaging during both engaged behavior and passive viewing, it was found that, unlike V1, most neurons in PPC responded exclusively during task engagement, with a strong bias toward target stimuli. After retraining mice on a reversed reward contingency, researchers found that most PPC neurons exhibited a dramatic shift in selectivity toward the new target stimulus. Together these results demonstrate an important role for mouse PPC in the flexible transformation of sensory inputs into motor commands.

Mapping specific sensory features to future motor actions is a crucial capability of mammalian nervous systems. The Sur laboratory investigated the role of V1, PPC, and frontal motor (fMC) cortices for sensorimotor mapping in mice during performance of a memory-guided visual discrimination task. Large-scale calcium imaging revealed that V1, PPC, and fMC neurons exhibited heterogeneous responses spanning all task epochs (stimulus, delay, response). Population analyses demonstrated unique encoding of stimulus identity and behavioral choice information across regions, with V1 encoding stimulus, fMC encoding choice even early in the trial, and PPC multiplexing the two variables. Optogenetic inhibition during behavior revealed that all regions were necessary during the stimulus epoch, but only fMC was required during the delay and response epochs. Stimulus identity can thus be rapidly transformed into behavioral choice, requiring V1, PPC, and fMC during the transformation period, but only fMC for maintaining the choice in memory prior to execution.

Susumu Tonegawa

Susumu Tonegawa is the Picower Professor in the Departments of Biology and Brain and Cognitive Sciences. His 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 role of two neuronal populations in the storage of contextual and temporal fear memory information was uncovered; and
- Memory failure in early Alzheimer's disease is caused by a failure of memory retrieval, rather than storage, and use of a long-term potentiation protocol could be a method for restoring "lost" memories.

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, researchers 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.

Entorhinal Cortical Ocean Cells Encode Specific Contexts and Drive Context-Specific Fear Memory

Forming distinct representations and memories of multiple contexts and episodes is thought to be a crucial function of the hippocampal-entorhinal cortical network. The hippocampal dentate gyrus and the CA3 area are known to contribute to these functions, but the role of the entorhinal cortex is poorly understood. Researchers in the Tonegawa laboratory showed that ocean cells, excitatory stellate neurons in the medial entorhinal cortex layer II that project into the dentate gyrus and CA3 area, rapidly form a distinct representation of a novel context and drive context-specific activation of downstream CA3 cells as well as context-specific fear memory. In contrast, island cells, excitatory pyramidal neurons in the medial EC layer II that project into the CA1 area, are indifferent to context-specific encoding or memory. On the other hand, ocean cells are dispensable for temporal association learning, for which island cells are crucial. Together, the two excitatory medial entorhinal cortex layer II inputs to the hippocampus have complementary roles in episodic memory.

Distinct Speed Dependence of Entorhinal Island and Ocean Cells, Including Respective Grid Cells

Entorhinal-hippocampal circuits in the mammalian brain are crucial for an animal's spatial and episodic experience, but the neural bases for different spatial computations remain unknown. The medial entorhinal cortex layer II contains pyramidal island and stellate ocean cells. Researchers performed cell type-specific Ca2+ imaging in freely exploring mice, using cellular markers and a miniature head-mounted fluorescence microscope. Both oceans and islands were found to contain grid cells in similar proportions, but island cell activity, including activity in a proportion of grid cells, was significantly more speed modulated than ocean cell activity was. Researchers speculate that this differential

property reflects island cells' and ocean cells' contributions to different downstream functions: island cells may contribute more to spatial path integration, whereas ocean cells may facilitate contextual representation in downstream circuits.

Memory Retrieval by Activating Engram Cells in Mouse Models of Early Alzheimer's Disease

Alzheimer's disease is a neurodegenerative disorder characterized by progressive memory decline and subsequent loss of broader cognitive functions. Memory decline in the early stages of Alzheimer's disease is mostly limited to episodic memory, in which the hippocampus has a crucial role. However, it has been uncertain whether the observed amnesia in the early stages of Alzheimer's disease is caused by disrupted encoding and consolidation of episodic information, or an impairment in the retrieval of stored memory information. Researchers showed that in transgenic mouse models of early Alzheimer's disease, direct optogenetic activation of hippocampal memory engram cells resulted in memory retrieval despite the fact that these mice are amnesic in long-term memory tests when natural recall cues are used, revealing a retrieval, rather than a storage, impairment. Before amyloid plaque deposition, the amnesia in these mice is age-dependent, which correlates with a progressive reduction in spine density of hippocampal dentate gyrus engram cells. Optogenetic induction of long-term potentiation at perforant path synapses of dentate gyrus engram cells restores both spine density and long-term memory. Researchers also demonstrated that an ablation of dentate gyrus engram cells containing restored spine density prevents the rescue of long-term memory. Thus, selective rescue of spine density in engram cells may lead to an effective strategy for treating memory loss in the early stages of Alzheimer's disease.

Li-Huei Tsai

Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences

The Tsai laboratory uses multidisciplinary approaches to study neuropathologies that affect cognitive function. Researchers focus on neurodegenerative disorders, such as Alzheimer's disease, with an additional interest in neurodevelopmental disorders, such as autism and Down syndrome. In the past, the Tsai laboratory deciphered the epigenetic control of gene expression as it affects cognitive function in the brain. Epigenetic modifications include those that impact 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. More 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.

Progress made in the past year focuses on using new technologies to determine neural circuitry affected by Alzheimer's disease and to ameliorate Alzheimer's disease–related pathology and symptoms.

Four-Dimensional Mapping of Network-Specific Pathological Propagation in

Alzheimer's Disease

CLARITY, a technology that renders tissue transparent and amenable to repeated three-dimensional immunolabeling and imaging, was developed by Kwanghun Chung and Karl Deisseroth. Through collaboration with the Chung laboratory, researchers in the Tsai laboratory optimized methods and mapped amyloid-beta (Aβ) aggregates at the whole-brain scale across disease stages in a mouse model of Alzheimer's disease. The spatially unbiased, temporally precise map demonstrates hierarchical susceptibility of increasingly large, memory-related brain networks to Aβ aggregate deposition. The four-dimensional nature of the map reveals that the subcortical nodes and white matter tracts of the Papez memory circuit exhibit unique, early vulnerability to Aβ aggregates. Finally, using large-volume labeling approaches, researchers confirmed the molecular findings by showing disease-specific Aβ aggregation in human samples from the early hub regions. Together, this data unites disparate observations of network-level deficits and identifies critical locations of early Aβ deposition in the brain. By linking molecular and network observations, researchers are beginning to provide biological explanations for the clinical manifestation of Alzheimer's disease. This perspective can guide earlier patient identification efforts and refine experimental approaches to developing cognitively efficacious treatments.

Gamma Oscillations Attenuate Amyloid Pathology and Trigger a Distinct Microglia Response in Mouse Models of Alzheimer's Disease

Gamma oscillations (20 to 50 Hz), a common local field potential signature in many brain regions, are generated by a resonant circuit between fast-spiking-PV-interneurons (FS-PV-interneurons) and pyramidal cells. Changes in gamma have been observed in several neurological disorders; however, the relationship between gamma oscillations and the cellular pathologies of these disorders is unclear. The Tsai laboratory collaborated with the Boyden laboratory and Professor Emery Brown to investigate this relationship, using the 5XFAD mouse model of Alzheimer's disease, and found reduced behaviorally driven gamma activity in these mice. Further, this phenotype was present before the onset of plaque formation or measurable cognitive decline. Researchers discovered that optogenetically driving FS-PV-interneurons at gamma frequency reduced levels of Aβ1-40 and Aβ1-42 isoforms in the hippocampus of 5XFAD mice. Furthermore, driving FS-PV-interneurons reduced enlarged endosomes and amyloid precursor protein cleavage intermediates in hippocampus. Gene expression profiling revealed an induction of microglia-specific genes associated with morphological transformation of, and increased, Aβ phagocytosis by microglia. Inspired by these observations, researchers designed a noninvasive light-flickering paradigm that induced gamma oscillations in visual cortex. The light-flickering paradigm profoundly reduced Aβ1-40 and Aβ1-42 levels in the visual cortex of pre-symptomatic mice and greatly mitigated the plaque load in symptomatic mice. A GABA-A antagonist completely blocked this effect—further evidence that GABAergic interneuron activity is essential for this neuroprotective gamma effect. Finally, the Tsai laboratory showed that gamma oscillations alleviated tau pathology in the TauP301S mouse model. Overall, these findings uncover a previously unappreciated function of the brain's gamma rhythms in neuroprotection by recruiting both neuronal and glial responses to mitigate the pathology associated with Alzheimer's disease. This work has potentially transformative implications for the treatment of Alzheimer's disease.

Histone Deacetylase 3 Associates with MeCP2 to Regulate FOXO and Social Behavior

In the realm of neurodevelopmental disorders that impact cognition, several recent studies from the Tsai laboratory, using both mouse models and human neurons, revealed novel mechanisms for defects in neuronal maturation and function associated with autism-spectrum disorders. One such study concerns HDAC3, MeCP2, and FOXO family transcription factors. Mutations in MECP2 cause the neurodevelopmental disorder Rett syndrome (RTT), and one critical function of MeCP2 involves the recruitment of HDAC3 to gene promoters and subsequent activation of FOXO proteins via HDAC3-dependent deacetylation. The RTT missense MECP2R306C mutation prevents MeCP2 interaction with HDAC3, and neuronal deletion of Hdac3 elicits similar phenotypes as does the MECP2 mutation: abnormal locomotor coordination, sociability, and cognition. Transcriptional and chromatin profiling revealed that HDAC3 positively regulates a subset of genes and is recruited to active gene promoters via MeCP2. HDAC3-associated promoters are enriched for the FOXO transcription factors, and FOXO acetylation is elevated in Hdac3 KO and Mecp2 KO neurons. Human RTT patient-derived MECP2R306C neural progenitor cells have deficits in HDAC3 and FOXO recruitment and gene expression. Gene editing of MECP2R306C cells to generate isogenic controls rescued HDAC3-FOXO-mediated impairments in gene expression. The data suggests that HDAC3 interaction with MeCP2 positively regulates a subset of neuronal genes through FOXO deacetylation, and disruption of HDAC3 contributes to cognitive and social impairment.

Kay Tye

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 modern neuroscience 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 Tye laboratory 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 that integrates electrophysiological, optogenetic, pharmacological, and imaging techniques to study the neural bases of behavior. Some of the research from the Tye laboratory has already been reported in a number of publications (e.g., Neuron in 2013 and the Journal of Neuroscience in 2014); this work described the identification of a novel pathway from the amygdala to the ventral hippocampus that can bidirectionally control anxiety-related behaviors and social interaction, respectively. In other work, the Tye laboratory examined the functional encoding dynamics of optogenetically identified midbrain-projecting lateral hypothalamic neurons during a reward-seeking task, and showed that lateral hypothalamic projections to the ventral tegmental area control compulsive sucrose-seeking behavior. This work was featured on the cover of Cell. The Tye laboratory has followed up on the mechanism of this phenomenon. The laboratory has also published another study (featured on the cover of Nature) that describes a circuit mechanism for differentiating positive and negative emotional associations, which they have also investigated using in vivo electrophysiological recordings in "phototagged" populations

of neurons. More recently, researchers have identified a population of dopamine neurons in the dorsal raphe nucleus that underlie the experience of social isolation. Together, researchers 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

Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology

Work in Matthew 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 had shown that the hippocampus reactivates memories of recent experience during sleep in what may be described as the animal correlate of dreaming. They 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. Researchers in the Wilson laboratory have also found that the 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 demonstrated the role of brain rhythms in enhancing memory performance.

Weifeng Xu

Picower Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences

Researchers in the Xu laboratory studies how experience shapes the excitatory neural circuit via the mechanisms underlying long-lasting changes in synaptic transmission (synaptic plasticity). They 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 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

Synaptic scaffold proteins connect transmembrane receptors to chaperone proteins and intracellular signaling components. It has been hypothesized that via specific interactions, the scaffold proteins control the proper signal transduction from the extracellular signal, such as neurotransmitter release, to intracellular signaling cascades critical for information encoding in the brain. The laboratory's functional analyses support this hypothesis that different membrane-associated guanylate kinase (MAGUK) scaffold proteins influence synapses differently in aspects including dependence on neuronal activity, receptor trafficking, and the kinetics of synaptic responses. However,

the overall landscape of how different scaffold proteins control synaptic content is missing. Researchers are now mapping the synaptic diversity and signaling specificity controlled by scaffold proteins, using quantitative proteomic and phosphoproteomic analysis focused on synapses. They have found that manipulations of MAGUK-family proteins PSD-95 and PSD-93 have convergent and divergent effects on synaptic contents, suggesting an antagonizing effect of PSD-95 and PSD-93 in regulating the glutamatergic synaptic function. The laboratory has also 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 Experience-dependent Plasticity and Learning and Memory

Calcium influx through neurotransmitter receptors and voltage-gated ion channels is essential for activity-dependent neural plasticity in the brain. The cellular response from calcium influx is normally mediated via processes dependent on the calcium-binding protein, Calmodulin (CaM). Dysregulation of calcium homeostasis is thought to contribute to neuropsychiatric diseases such as schizophrenia, mental retardation, and normal aging. Neurogranin, a CaM-binding protein, is centrally localized in principal neurons throughout the cortex and the 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. By studying the regulation and functional significance of neurogranin in the nervous system, we start to elucidate the molecular mechanisms underlying experience-dependent neural plasticity. Three lines of research have been developed in this area:

- Experience-dependent upregulation of neurogranin in hippocampus facilitates long-term potentiation and contextual memory formation. This experience-dependent upregulation is because of activity-dependent translation of neurogranin, which is required for contextual memory formation.
- In mouse primary visual cortex, the experience-dependent pruning of glutamatergic synapses and maturation of AMPAR-silent synapses together maintain AMPAR-transmitting synapses at equilibrium during the critical period. The sensory experience coordinates these experience-dependent processes through neurogranin-dependent regulation to functionally optimize neural circuits.
- Changes in neurogranin levels lead to shifts in the phosphoproteome, and impact spike-timing dependent plasticity and LTP by regulating protein phosphatase 2B (PP2B) activity. The dynamics of neurogranin levels at different behavioral or pathological states can influence the basal phosphorylation state of neurons by tuning PP2B activity; hence the expression of synaptic plasticity.

Li-Huei Tsai
Director
Picower Professor of Neuroscience