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 neuroscience of 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

Earl K. Miller gave the 2009 A.J. Carlson Memorial Lecture at the University of Chicago, was a 2010 National Institutes of Health (NIH) recipient of the MERIT Award, and was a Biomed Distinguished Lecturer at the University of Leuven.

Li-Huei Tsai was the recipient of the Glenn Foundation Award for her research in biological mechanisms of aging. She gave the 2009 Cantoni Lecture at NIH.

Mriganka Sur received a top 50 alumni award from the Indian Institute of Technology and was the annual award lecturer at the University of Newcastle's Institute of Neuroscience in the United Kingdom. In addition, he was the chair of the Kavli National Academy of Sciences Frontiers in Science Symposium in China; the keynote lecturer at the Bernstein Conference on Computational Neuroscience in Frankfurt, Germany; and a lecturer at the Nobel Conclave and Symposium, Indian Institute of Information Technology, Allahabad, India.

Research Breakthroughs

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

Research affiliate Guosong Liu of Susumu Tonegawa's laboratory showed that increasing one's intake of magnesium, an essential mineral found in dark leafy vegetables and certain fruits, beans, and nuts, may help combat memory lapses associated with aging. Mice given extra doses of a new magnesium compound had better working memory, long-term memory, and learning ability.

Li-Huei Tsai has developed a powerful new Alzheimer's model using mice and is working to better understand and stop this disease that robs people of their memories, independence, and personalities.

Carlos Lois has discovered that when it comes to new neurons in the adult brain, the squeakiest wheels get the grease. Any perturbation that increases the activity of neurons seems to enhance the likelihood of their survival. New discoveries in this area are likely to have a significant influence on cell replacement therapies.

Recent research out of Matt Wilson's laboratories is focusing on the age-old question "What are dreams?" Also, researchers in Wilson's laboratories have found that rats use a mental "instant replay" of their actions to help them decide what to do next, shedding new light on how animals and humans learn and remember.

Mark Bear's laboratories are going back to brain basics to generate promising treatments for autism, mental retardation, and Alzheimer's disease.

Multitasking has rapidly taken over contemporary lives, to the point where one appears lax doing just one thing at a time. New research from Earl Miller's laboratory suggests that when looking for something in one's environment, one's attention scans just one thing at a time, using a serial, as opposed to a parallel, process whose clock speed is controlled by brain waves or "neuron population oscillations." The research done in Miller's laboratory on monkeys suggests that the brain neurons involved in learning may process information more effectively after a success than after a failure, which in turn leads to improvements in behavior.

Elly Nedivi's laboratory is working on an actively regulated gene that is important for learning.

Personnel

In addition to 10 faculty members, the Picower Institute consists of other researchers, students, and technical and administrative support personnel. More than 230 community members participated in Picower Institute activities during the report period: 10 faculty members, 9 senior researchers, 12 visiting scientists/scholars, 71 postdoctorates, 31 undergraduates, 22 graduate students, 57 research and technical staff, and 24 administrative and service staff.

Items of note during the academic year included the following:

Yasunori Hayashi accepted an appointment at the RIKEN Brain Science Institute in Japan as of July 1, 2009.

Li-Huei Tsai accepted the directorship of the Picower Institute effective July 1, 2009.

Myriam Heiman accepted a junior faculty position within the Picower Institute (and the Department of Brain and Cognitive Sciences [BCS]) as an assistant professor.

John Maher joined the Picower Institute in January 2010 as the fiscal officer. John is a certified public accountant who brings with him many years of experience having worked for MIT in the Department of Biology.

Najat Kessler joined the Picower Institute in March of 2010 as the events/web coordinator. Najat brings with her years of web and event management experience.

David Vaughn joined the Picower Institute in June 2010 as the assistant director of administration. David comes to Picower with extensive experience in health care and operations management.

Kelly Murray recently joined the Picower Institute as the human resources administrator. Kelly brings a breadth of experience having worked for MIT in the Payroll Office and for the Picower Institute in its early years.

Morgan Sheng resigned in spring 2010.

Resource Development

Resource development continues to be a high priority at the Picower Institute. Fundraising activities included one-on-one individual meetings and group presentations with prospects in Massachusetts, New York, California, and Florida. Both Li-Huei Tsai and Mriganka Sur traveled with Martha Ruest to meet these potential donors. Additionally, many of the Picower Institute faculty gave their time for prospect and donor meetings both at MIT and in the community.

Several resource development events were produced to build awareness of and donor interest in the Picower Institute faculty and their work. The Department of Brain and Cognitive Sciences hosted a lecture featuring professor Earl Miller and his presentation "The Prefrontal Cortex: Understanding the Brain's Executive" in a new breakfast series for donors and alumni. More than 75 people attended. Follow-up stewardship was conducted for all prospect visits and events, and approximately 12 new prospects at the leadership level have been qualified.

New leadership gifts to the Picower Institute included a $25,000 individual contribution to Li-Huei Tsai's laboratory for Alzheimer's research, a $50,000 individual contribution to Mark Bear's laboratory, a $100,000 individual gift to support Earl Miller's laboratory, and several smaller gifts from new prospects.

A search for a senior resource development officer to replace Martha Ruest (who left MIT in February 2010) was successfully completed in June 2010 with the hiring of Barbara Vejvoda, a development professional with extensive academic and health care fundraising experience.

Media Recognition

The Picower Institute issued 10 MIT press releases during the reporting period. Articles appeared in the following major print media: the *Boston Globe*, *Science Daily*, the *Miami Herald*, *Medical News Today*, the *Financial Times*, the *Austin American Statesman*, the *Atlanta Journal Constitution*, the *Telegraph* (United Kingdom), *Technology Review*, *Forbes India*, and the *Times of India*. Picower Institute research breakthroughs were also broadcast on *NOVA*, Fox News, and BBC's *Horizon* and via the web on MSNBC.com, Foxnews.com, Boston.com, Dailymail.co.uk, Insciences.org, EarthSky.org, The-Scientist.com, CNNhealth.com, and WebMD.com.

Programs and Activities

The Picower Institute was founded on the premise that collaboration among disciplines is an integral component of its research philosophy. To facilitate these collaborative

interactions, the Picower Institute follows a rigorous calendar of formal lectures, conferences, and workshops as well as 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 in 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 Picower Foundation's generous support of the neurosciences at MIT. Each lecture features work of a current leader in the area of brain research. This year's lecturer was Thomas Sudholf from Stanford University. His talk, "How Ca^{2+} Triggers Neurotransmitter Release," took place on April 22, 2010.

The Picower Institute colloquia bring 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, colloquium speakers were Eric Klann of New York University, Mark Hubener of the Max Planck Institute of Neurobiology, and Pascal Fries of the Ernst Strungmann Institute.

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 biweekly series of informal talks during the academic year that give postdoctorates and graduate students from across the Picower Institute a chance to share their latest, often prepublished, research with colleagues. 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 targeted to the Picower Institute's postdoctorate community provided resources to support activities that build community and enrich interactions between postdoctoral colleagues and future associates. The postdoctorates convened a series of informal talks and social events and developed a website detailing their research interests and community activities.

The "Picower Power Lunch," a monthly Picower Institute faculty gathering, allows faculty and guest speakers to informally relate recent research findings or present new ideas.

Each year, after the close of the academic year, the Picower Institute hosts an annual retreat for its community members. The third annual Dana and Betty Fisher Retreat of the Picower Institute for Learning and Memory was held on June 15, 2010, in Needham. More than 140 researchers attended the event, which included nine laboratory research presentations, a highly interactive poster session (with 15 submissions), and a keynote address by renowned neurobiologist Amy Arnsten of Yale University.

Research Initiatives

The advent of human induced pluripotent stem (iPS) cells has heralded a new generation of clinical and basic research into human disorders. Patient-derived skin fibroblast cells are reprogrammed into iPS cells, allowing researchers to directly examine a wide variety of diseases directly in human cells. In addition, iPS cells have remarkable therapeutic potential, as they can be differentiated into multiple cell types, including neurons, and can be transplanted back into the donor without the risk of an immune response. Cells derived from patients can also be used to screen novel therapeutic compounds, and, as these cells reflect the genetic profiles of their donors, they can be used to study the mechanisms of multiple neuropsychiatric and neurodegenerative disorders.

The creation of a common iPS facility in the BCS complex will provide a powerful incentive for different labs to collaborate and exchange ideas. This facility will integrate the various research goals of members of the Picower Institute, the McGovern Institute for Brain Research, and the Department of Brain and Cognitive Sciences. The various BCS, McGovern, and Picower laboratories have expertise and experience with different experimental protocols, which, when combined in a collaborative manner to the study of human cells, will result in accelerated progress in this novel, dynamic, and competitive field. This exciting resource will soon be available to MIT researchers.

The Viral Vector Core Facility was launched in fall 2008 by the Picower Institute in partnership with the McGovern Institute for Brain Research and with the support of an anonymous donor. Dr. Rachael Neve, an internationally renowned expert in viral vector research with over 250 publications, assumed the directorship of the facility. Designed to become a self-supporting service facility over a period of three years, the Viral Vector Core Facility is a resource for MIT's neuroscience community and will be available to others across MIT and beyond in the future. Viral gene delivery is a powerful adjunct to transgenic mice for sophisticated manipulations of neuronal function. The facility initially offered modified herpes simplex virus (HSV) for delivery of genes into neurons in the brain; this resource is not available anywhere else in the world. Dr. Neve has since developed two additional viral vectors with features that complement those of the HSV vector, and a fourth is in the pipeline. This technology allows research laboratories to answer, in a uniquely direct way, basic questions about how specific types of neurons contribute to brain function and behavior. The facility has attracted many users from MIT with diverse research interests; all are members or affiliates of the Picower Institute for Learning and Memory or the McGovern Institute for Brain Research. More than 20 different genes for investigators in the McGovern Institute and over 30 different genes for investigators in the Picower Institute have been subcloned into the three viral vectors currently available and packaged into viruses. The use of these viruses to understand memory and cognition will provide the basis for new treatments of neurological and psychiatric disorders.

Faculty Research Summaries

The scholarly excellence of the Picower Institute faculty is reflected in distinguished publication records. During the reporting period, Picower Institute faculty published seven articles in hallmark science journals (*Science*, *Neuron*, *Cell*, and *Nature*) and 30 peer-reviewed articles overall.

Picower Institute faculty research areas are summarized below.

Li-Huei Tsai's laboratory uses a combination of molecular/cellular, genetic, and behavioral approaches to study Alzheimer's disease and psychiatric and developmental disorders. Tsai's laboratory developed an innovative mouse model exhibiting the onset of Alzheimer's symptoms in a fraction of the time previously possible. Using this model, Tsai explored novel therapeutic approaches to combat cognitive impairment resulting from neurodegeneration. Tsai and colleagues reported a remarkable recovery of long-term memory by housing the mice in an enriched environment or treating them with nonselective histone deacetylase (HDAC) inhibitors that induce chromatin remodeling. Recently, she and colleagues identified HDAC2 as the major histone deacetylase that regulates synaptic plasticity and memory formation. Further experiments suggest that HDAC2 serves as the major target for the nonselective HDAC inhibitors in facilitating learning and memory. Tsai also made major advancements in understanding the biology of neuropsychiatric disorders. She found an interaction between the schizophrenia candidate gene DISC1 and Wnt signaling in the regulation of neural progenitor proliferation that provides fundamental insights into the role of brain development in schizophrenia. In collaboration with Chris Moore at the McGovern Institute for Brain Research, Tsai used the light-sensitive bacteriorhodopsin channelrhodopsin-2 (ChR2) to drive the activation of parvalbumin-positive interneurons in the somatosensory cortex, inducing gamma oscillations and the sharpening of sensory responses. This work provided the first causal evidence for the induction of distinct network activity states by activation of a specific cell type in the brain. Her work will continue to incorporate in vivo optogenetics as her lab attempts to restore memory deficits resulting from neurodegeneration. Finally, in a recent publication, Tsai demonstrated a role for the SIRT1 protein in modulating cognition. This finding supplements her earlier work, which showed a role for SIRT1 in neuroprotection, and uncovers a novel mechanism by which SIRT1 influences synaptic plasticity and memory via regulation of a microRNA, miR-134.

Mark Bear's laboratory is using knowledge gained from studies on visual functioning to investigate ways in which recovery of function can be promoted. The modification of synapses by neural activity has been proposed to be the substrate for experience-dependent brain development, learning, and recovery of visual function after brain injury. The effectiveness or "strength" of synaptic transmission can be persistently modified in response to defined patterns of presynaptic and postsynaptic activity. Well-studied examples of this type of synaptic plasticity are long-term potentiation and long-term depression. Can the current understanding of these mechanisms be exploited to strengthen brain connections that may have been weakened or impaired by sensory

deprivation, disease, or injury? Theoretically motivated research on the visual cortex has suggested ways to promote synaptic potentiation. The theoretical concept is that the type and extent of synaptic plasticity caused by patterns of activity depend critically on the recent history of synaptic or cellular activity. Studies involving the visual cortex strongly support this concept and have suggested a mechanism for "metaplasticity"—the plasticity of synaptic plasticity—based on activity-dependent modification of the structure and function of N-methyl-d-aspartate (NMDA) receptors.

A myriad of mechanisms have been suggested to account for the full richness of visual cortical plasticity. In collaboration with Mriganka Sur's laboratory, researchers in Bear's laboratory found that a visual cortex lacking the protein Arc is impervious to the effects of deprivation or experience. The remarkable new view that emerges from these studies of the visual cortex is that, by adolescence, excitatory synapses are rendered essentially immutable by experience or deprivation if Arc is not expressed in their postsynaptic target. Despite this profound defect in acquired properties, the innate organization and levels of visual responsiveness appear to be normal in Arc knockout (KO) mice. It appears that a requirement for Arc paints a bright line that separates the contributions of "nurture" (those dependent on the quality of sensory experience) from the contributions of "nature" (those dependent on genetic instructions alone) with respect to the development of glutamatergic synaptic connections in the cortex.

Fragile X syndrome is the leading inherited cause of mental retardation and autism. The Bear laboratory's recent advances in mechanistic understanding of the disease have led to identification of the metabotropic glutamate receptor (mGluR) as a therapeutic target for the disease. These studies have revealed that core defects in multiple animal models can be corrected by down-regulation of mGluR5 signaling. Although it remains to be determined whether mGluR5 antagonists or related approaches will succeed in humans with fragile X, the progress in this area stands as a strong testament to the power of applying knowledge of basic neurobiology to understand pathophysiology in a genetically validated model of human psychiatric disease.

J. Troy Littleton's laboratory studies the mechanisms by which neurons form synaptic connections, how synapses transmit information, and how synapses change during learning and memory. The laboratory also studies how alterations in neuronal signaling underlie several neurological diseases, including epilepsy, autism, and Huntington's disease. Recently, the laboratory discovered an important presynaptic pathway for the regulation of activity-dependent synaptic growth that is controlled by endosomal trafficking of synaptic growth receptors. The identification of new endosomal regulators of growth receptor trafficking has revealed the underlying mechanisms by which activity-dependent growth signals are turned on and off during synaptic activity. New synapse formation and synaptic rewiring are key elements of plasticity in the developing and adult brain. Similar to many species, modulation of synapse formation in *Drosophila* has been implicated in learning and memory. Recent work has suggested that several known autism-causing mutations identified in humans alter endosomal trafficking, implicating this pathway in human disease. The laboratory is characterizing several of these autism-linked proteins to define how their dysfunction alters endosomal processing of synaptic growth signals. Together, these studies are beginning to define the molecular mechanisms by which neuronal activity modifies synaptic connections.

Carlos E. Lois's laboratory is interested in the assembly of neuronal circuits and the genetic control of brain development and function. The laboratory focuses on the process of neuron replacement in the vertebrate brain and seeks to understand how new neurons integrate into the circuits of the adult brain and their role in information processing and storage. To address these questions, the laboratory develops new technologies to genetically manipulate the development and biophysical properties of neurons. The laboratory recently developed a method to genetically manipulate the electrical activity of neurons in the brain to increase or decrease their excitability. With this method, it was found that new neurons generated in the brain of postnatal animals have a limited ability to regulate their synaptic activity when rendered hyperexcitable. This finding has important implications for understanding the pathological basis of epilepsy in humans. In addition, the Lois laboratory has discovered a new form of migration by which cells navigate through the adult brain. Using in vivo two-photon imaging, the laboratory has found that immature neurons migrate long distances in the absence of any scaffold, following tortuous, nonlinear trajectories in a searchlike manner until they cease their migration and start establishing synaptic contacts. Finally, the laboratory developed a transgenic technology based on enhancer trapping in which a viral vector integrates into a cell's genome and recapitulates the expression pattern of the endogenous gene that is near its integration site. Using this method, they have generated transgenic lines of mice that display gene expression in selective cell types in the brain. Analysis of one of the transgenic lines generated has demonstrated that astrocytes are generated in columnar structures in the cortex. This finding has implications for the organization of the brain during development, as astrocytes are the most abundant cells in the mammalian brain, and they are involved in key physiological processes such as regulation of brain blood flow and formation of the blood-brain barrier.

The overarching goal of Earl K. Miller's laboratory is to build on what has been learned from classic single-electrode neurophysiology to understand cognitive functions in a broader context, as a product of interactions between different 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 the kind of sophisticated, flexible, rule-based behaviors at which humans and monkeys are so adept. In the past year, the Miller laboratory has made a number of discoveries. For example, they found that individual neurons in the monkey prefrontal cortex can "multitask" and play a role in representing very different categories (cat vs. dog, sedan vs. sports car). At the same time, the degree of multitasking depends on cognitive demands, namely the degree to which the different categories can be confused. This may explain why normal human cognition is so flexible; it may also explain its inflexibility in diseases such as autism. In addition, Miller's laboratory found that when monkeys hold two pictures "in mind" (i.e., in working memory) simultaneously, neural activity associated with the two pictures lines up on different areas of 32 Hz "brain waves" across the neuron population. This may explain humans' severe limitations in thinking multiple thoughts at the same time, and it indicates that dysfunction of these mechanisms may account for the disordered thought of schizophrenia.

Elly Nedivi's laboratory studies the cellular mechanisms that underlie activity-dependent plasticity in the developing and adult brain through identification and characterization of the participating genes and the proteins they encode. *cpg15* (neuritin) encodes a small extracellular ligand that was initially discovered in the lab's screen for activity-regulated genes in the rat hippocampal dentate gyrus (DG). The CPG15 protein promotes dendritic and axonal arbor growth and synapse maturation. To study the in vivo role of *cpg15* in the developing brain, the lab generated a *cpg15* KO mouse. Overall sensory and motor function, as well as gross brain anatomy and dendritic morphology, was normal in these mice at eight weeks of age. Nevertheless, *cpg15* KO mice had difficulty with learning tasks. Nedivi's lab examined whether functional deficits in the adult KO mouse might derive from the effects of CPG15 on synapse formation and maturation by performing electron microscopy in different subfields of the hippocampus. They found that neurons in the DG of *cpg15* KO mice initially form fewer spine synapses than wild-type neurons, but these synapses have longer postsynaptic densities and undergo little remodeling in the adult. Consistent with electron microscopy data, at two months of age, DG granule cells in *cpg15* KO mice had lower miniature excitatory postsynaptic current (mEPSC) frequencies and smaller mEPSC amplitudes than wild-type controls, while no difference was seen in CA1 at this age. To more closely examine the role of CPG15 in spine synapse development, hippocampal cultures were prepared from *cpg15* KO and wild-type embryos and sections of spiny dendrites were imaged twice, with a three-day interval. Compared to wild-type, *cpg15* KO cultures exhibited more spine turnover and a smaller percentage of persistent spines. This deficit could be rescued by addition of recombinant CPG15. These results suggest that CPG15 acts to stabilize dendritic spines and arbors, perhaps through selective stabilization of active synapses.

Morgan H. Sheng's laboratory is interested in the molecular mechanisms by which synapses in the brain change their strength and connectivity in response to experience. Altered synapse structure and function appear to underlie many human brain disorders ranging from autism to Alzheimer's disease. A cardinal feature of Alzheimer's disease is the weakening and loss of synapses. The Sheng laboratory discovered that a well-established model of synapse weakening and shrinkage (long-term depression) shares the same molecular mechanisms as apoptosis (or programmed cell death). Thus, synapse depression and elimination might be considered local "synaptic apoptosis," unaccompanied by cell death of the neuron as a whole. The Sheng lab also discovered that calcium-calmodulin-dependent protein kinase II (CaMKII) plays a structural role by recruiting proteasomes to stimulated synapses. This new function provides an explanation of why CaMKII is present in such high abundance at synapses. Both studies, published in *Cell* in 2010, were highlighted in commentaries in other journals.

Mriganka Sur's laboratory uses cutting-edge technologies for imaging cells and molecules in the intact brain in order to reveal their roles in synaptic plasticity and cortical function. Combined with novel probes, these methods have revealed unexpected mechanisms of cortical plasticity, the role of specific cell classes in cortical circuits, and mechanisms of brain disorders. In the past year, his laboratory has discovered the function of a key molecule, Arc, in regulating synaptic plasticity in the visual cortex. Removing Arc renders the visual cortex impervious to the effects of visual experience or deprivation.

Using specific transgenic mice, his laboratory discovered that a crucial class of inhibitory neurons in the cortex that expresses parvalbumin and targets the soma of other neurons has precise responses that help shape the responses of targets. After analyzing mice deficient in specific autism genes and examining the effects on signaling molecules at synapses, Sur's laboratory proposed a therapy for Rett syndrome that has entered clinical trials. This discovery points to an exciting breakthrough in autism research.

Susumu Tonegawa's laboratory seeks to understand the brain mechanism underlying memory and its disorders. Among the lab's major discoveries is identifying a protein and neuronal circuits in the hippocampus that prevent a memory from remaining at the "tip of the tongue," a common memory recall deficit pronounced by normal aging and by Alzheimer's disease. Tonegawa's laboratory combines the cutting-edge technologies of genetic engineering, electrophysiology, and behavioral methods. Using a genetic technology it developed, Tonegawa's research team created mouse strains in which one of about 30,000 mouse genes and the protein created are knocked out only in a particular type of neuron of a highly restricted part of the brain. By observing the physiological and behavioral deficits of these mice, the Tonegawa laboratory, in collaboration with Matthew A. Wilson's laboratory, discovered that a single gene encoding a neurotransmitter receptor—the NMDA receptor in the tiny hippocampal area CA3—is critical for two major memory functions: the ability to rapidly form memories of episodes or events in day-to-day life and the ability to recall the details of the memory previously formed with scant informational cues (a phenomenon called "pattern completion"). Most recently, using an analogous approach, Tonegawa's laboratory discovered that the NMDA receptor in another part of the hippocampus, the DG, plays a crucial role in the animal's ability to acquire similar events as distinct memories (a phenomenon called "pattern separation"). This discovery also provides an intriguing explanation for the phenomenon of déjà vu and has been widely publicized in both professional journals and the popular press (e.g., *Time* magazine). Another recent discovery made in Tonegawa's laboratory that described a novel method to cure fragile X mental retardation and some forms of autism in a mouse model has been widely publicized as well.

In addition, Tonegawa's laboratory recently invented a novel mouse genetic engineering technology that permits a blockade of neurotransmitter release from a specific type of brain cell. Applying this technique to the major pathway within the hippocampus (CA3 to CA1), Tonegawa's laboratory demonstrated that this hippocampal pathway plays a crucial role in rapid acquisition of fear-associated memory but is dispensable for slow acquisition of spatial memory by repeated exposures. They also demonstrated that the consolidation of fear memory into a long-lasting form requires repeated activation of relevant CA1 neurons during slow-wave sleep. This genetic technology (dubbed DICE-K) promises to be powerful in the dissection of the functions of neural circuits—neural circuit genetics. This past year, Tonegawa's laboratory has continued to study the brain circuit mechanisms underlying memory. A widely held memory consolidation theory posits that memory of events and space is initially stored in the hippocampus in a time-limited manner and is consolidated in the neocortex for permanent storage. Although studies have demonstrated that posttraining hippocampal lesions result in temporally graded amnesia, the precise hippocampal circuits and mechanisms involved

in remote memory storage remain poorly understood. To investigate the role of the trisynaptic pathway, one of the two major excitatory circuits of the hippocampus, in the consolidation process they used the CA3-TeTX transgenic mouse, in which CA3 output can be specifically and inducibly controlled. Tonegawa's laboratory found that posttraining blockade of CA3 output for up to four weeks impairs the consolidation of contextual fear memory. Moreover, in vivo hippocampal recordings revealed reductions in the intrinsic frequency of CA1 ripples and a significant decrease in the experience-dependent enhancement of the ripple-associated coordinated reactivation of CA1 cell pairs during postrun slow-wave sleep or awake quiescent periods in the mutant mice. Collectively, these results suggest that the posttraining integrity of the trisynaptic pathway and the ripple-associated reactivation of the hippocampal memory engram are crucial for memory consolidation.

Work in Matthew A. Wilson's laboratory continues to focus on the hippocampus's role in the formation, maintenance, and use of memory in the mammalian nervous system during awake and sleep states. Recent experiments showed that while animals stop briefly in a maze, they rapidly replay or "think" about both past and future paths that they have taken or might take in a manner that is very similar to the reactivation of memories seen during sleep. This finding suggests that the mechanisms of thinking and the mechanisms of dreaming may be directly related and is consistent with recent evidence in humans that suggests that the hippocampus is involved in processing memories of the past as well as imagining future events. Current work seeks to characterize the detailed structure of brain activity as rats navigate and contemplate such mazes, and the lab has successfully demonstrated the ability to reconstruct the content of this activity, providing a potential window into the process of thought itself.

Weifeng Xu's laboratory aims to elucidate the molecular mechanisms of activity-dependent modifications of neuronal properties (neural plasticity), including synaptic efficacy and neuronal excitability. This activity-dependent plasticity is essential for the immense computational power of the neuronal network in terms of information processing and storage. Dysregulation of neuron excitability and synaptic efficacy is often manifested in neurological and psychiatric disorders and is thought to underlie some of the cognitive impairment and dysfunction often seen in these diseases. Using hippocampal organotypic slice cultures as a model system, laboratory researchers manipulate genes in single mature neurons and directly measure the effects of molecular manipulations on electrophysiological properties using simultaneous dual whole-cell patch clamp techniques. These measures include intrinsic neuronal excitability, signal integration and propagation, and synaptic plasticity, features that are important for information processing in the neuronal network. Results from these experiments will reveal the precise function and interplay of molecular components involved in neural plasticity.

Two lines of research are conducted in Xu's laboratory. First, using the molecular replacement approach, the laboratory has shown that the members of the postsynaptic scaffold DLG-MAGUK family proteins play distinct roles in regulating synaptic functions, preferentially increasing synapse numbers, increasing synaptic strength, or both. This functional diversity may underlie their specific functional significance during

development and experience-dependent plasticity. Ongoing research aims to further examine the molecular determinant of this functional diversity and its implications for synaptic plasticity. The second area of research involves calcium (Ca) and Ca-binding protein calmodulin (CaM), which are important messengers mediating electrical signals to cellular signaling. Using lentivirus-mediated knockdown and overexpression, Xu's laboratory studies the functional impact of manipulating Ca/Ca-CaM dynamics on neuronal properties. Laboratory researchers found that decreasing the levels of an apo-CaM binding protein (neurogranin) leads to more spike adaptation, possibly as a result of homeostatic compensation. Because the neurogranin level in neurons is dynamically regulated depending on activity levels, this pathway may contribute to activity-dependent regulation and modulation of neuronal network activity. Ongoing research aims to analyze the specific elements underlying this increased spike adaptation and further examine its functional implications for network activity. The outcomes of these studies will provide targets for pharmacological interventions for patients with neurodegenerative diseases and psychiatric disorders.

Li-Huei Tsai
Director
Picower Professor of Neuroscience

More information about the Picower Institute for Learning and Memory can be found at http://web.mit.edu/picower/.