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 was appointed 2009 co-director of the Center of Excellence for Learning in Education, Science, and Technology at the National Science Foundation Science of Learning Center. He was the 2009 Engineering Distinguished Lecturer at the National Science Foundation, was the plenary lecturer at the International Conference on Cognitive and Neural Systems, gave the Carlson Lecture at the University of Chicago, and was the keynote speaker at the meeting of the Comparative Cognition Society.

Mriganka Sur was elected a fellow of the American Association for the Advancement of Science and was named the inaugural holder of the Paul E. Newton professorship of neuroscience. He delivered the Darwin Bicentennial Lecture at the National Institute of Immunology, India; the Collège de France Lecture, Paris; the convocation address at the Indian Statistical Institute; the Institute of Neuroscience Lecture at the University of Newcastle, England; and keynote lectures at various scientific meetings. He received the Founder's Medal from the National Brain Research Center, India.

Li-Huei Tsai was elected a fellow of the American Association for the Advancement of Science. She was also a recipient of the National Institutes of Health (NIH) Cantoni Lecture Award for 2009.

Susumu Tonegawa delivered the 2008 University College of London Prize Lecture in Clinical Science.

As of July 1, 2008, Matthew A. Wilson became the Sherman Fairchild professor in neurobiology and the associate department head of the Department of Brain and Cognitive Sciences.

Weifeng Xu is a current recipient of an NIH Pathway to Independence Career Development Award.

Research Breakthroughs

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

Research affiliate Mariko Hayashi of Yasunori Hayashi's laboratory showed how a protein implicated in cognitive disorders maintains and regulates brain cell structures

that are key to learning and memory. The work could lead to new treatments for autism, mental retardation, and fragile X syndrome, which researchers believe are tied to abnormalities in synapses, the junctures through which neurons communicate.

Carlos E. Lois's laboratory found that using adult stem cells to replace neurons lost due to brain damage and disease could be more difficult than previously thought because newly formed brain cells receive messages before they are capable of sending them. The work, which concludes that adding new neurons to existing circuits would be akin to trying to integrate a new memory card into a running computer, has implications for treating conditions such as Alzheimer's and Parkinson's diseases and spinal-cord trauma.

Elly Nedivi and colleagues found that a type of neuron implicated in autism spectrum disorders remodels itself in a strip of brain tissue as thick as only four sheets of tissue paper. The work sheds new light on the potential flexibility of cerebral cortex circuitry and architecture in higher-level brain regions that contribute to perception and cognition.

Mriganka Sur pinpointed two genes that cause autism-like symptoms in mice, showing for the first time that multiple, interacting genetic risk factors may influence the severity of autistic symptoms. The work could lead to drugs targeting signaling mechanisms between the two interacting genes responsible for some symptoms of autism spectrum disorders. In separate work in collaboration with the Whitehead Institute for Biomedical Research, Sur also determined that a molecule that promotes brain development could serve as a possible treatment for Rett syndrome, the most common form of autism in girls.

Susumu Tonegawa demonstrated for the first time the molecular link between postexperience sleep and the establishment of long-term memory of that experience. The work, at the RIKEN-MIT Center for Neural Circuit Genetics, has a profound implication in the century-old search for the purpose of sleep.

In separate studies, Li-Huei Tsai's laboratory published findings related to Alzheimer's disease and schizophrenia. Tsai's work helps explain the perplexing behavior of some cells in the hippocampus, thought to be the center of learning and memory in the brain. In Alzheimer's disease, stroke, and other neurodegenerative conditions, some neurons suddenly start to replicate their DNA as if they were about to divide.

Focusing on a gene known as *DISC1* (short for "disrupted in schizophrenia 1"), Tsai discovered that a conserved signaling pathway, when interfered with, contributes to the etiology of psychiatric disorders and found that inhibiting a key brain enzyme in mice reversed schizophrenia-like symptoms.

A separate study from the Tsai laboratory, conducted with the McGovern Institute for Brain Research, used new technology to induce high-frequency brain waves—known as gamma oscillations and crucial to consciousness, attention, learning, and memory—by shining laser light directly onto the brains of mice. The research helps explain how the brain produces gamma waves and provides new evidence of the role they play in regulating brain functions—insights that someday could lead to new treatments for a range of brain-related disorders.

Tsai and colleagues pinpointed the gene responsible for a 2007 breakthrough in which mice with symptoms of Alzheimer's disease regained long-term memories and the ability to learn. In the latest development, Tsai found that drugs that work on the gene *HDAC2* reverse the effects of Alzheimer's disease and boost cognitive function in mice.

Personnel

In addition to 11 faculty members, the Picower Institute consists of other researchers, students, and technical and administrative support personnel. More than 245 community members participated in Picower Institute activities during the report period: 11 faculty members, 11 senior researchers, 6 visiting scientists/scholars, 69 postdoctorates, 48 graduate students, 26 undergraduates, 60 research and technical staff, and 17 administrative and service staff.

Items of note during the academic year include the following:

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

Morgan Sheng took a two-year leave of absence from MIT in fall 2008.

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

Weifeng Xu joined the Picower Institute (and the Department of Brain and Cognitive Sciences) in January 2009 as an assistant professor.

Resource Development

Major resource development activities during the past year included a jointly sponsored May 4, 2009, event entitled "Brains on Brains," which brought alumni and prospective donors together with faculty members from the Picower Institute, the Department of Brain and Cognitive Sciences, and the McGovern Institute for Brain Research to discuss the latest research on autism, diseases of aging—including Alzheimer's disease—and psychiatric disorders and diseases. During the year, Picower faculty members also met with MIT alumni and other prospective donors to explore giving opportunities, and Picower Institute faculty were featured at an event hosted by engineering professor Sanjay Sarma as well as the School of Science "Breakfast Series."

Media Recognition

The Picower Institute issued 15 MIT press releases in the reporting period. Articles appeared in the following major print media: *Business Week*, *Forbes*, *Newsweek*, *The New York Times*, *The New Yorker*, *Telegraph* (UK), *US News and World Report*, and *The Washington Post*. Picower Institute research breakthroughs were also broadcast on National Public Radio, ABC Radio, the Australian Broadcasting Corporation (ABC News Radio), and BBC News.

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 about learning and memory mechanisms in the brain offer to science and society. Ongoing programs and activities are described below.

Held annually, the Picower Lecture was named to honor and recognize the generous support of The Picower Foundation for neurosciences at MIT. Each lecture features work of a current leader in the area of brain research. This year's lecturer was Hannah Monyer of the University of Heidelberg. Her talk, entitled "GABAergic Interneurones: Their Role in Network Synchrony and Cognitive Behavior," took place on December 11, 2008.

The biweekly Picower Institute Seminar 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, seminar speakers were Sheena Josselyn of the University of Toronto; Joshua Trachtenberg of the University of California, Los Angeles; Joshua Gold of the University of Pennsylvania; Naoshige Uchida of Harvard University; Robert Reenan of Brown University; Mark Schnitzer of Stanford University; Fritjof Helmchen of the University of Zurich; Dax Hoffman of the National Institutes of Health; Christian Rosenmund of Baylor College of Medicine; Thomas Clandinin of Stanford University; Lucia Jacobs of the University of California, Berkeley; Mark Mayford of the University of San Diego, Scripps Institute; Grae Davis of the University of California, San Diego; Neal Cohen of the University of Illinois; and Michael Ehlers of Duke University.

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.

This past year, a new 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.

A monthly Picower Institute faculty "Sushi Chalk Talk" 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 Dana and Betty Fisher Retreat

of the Picower Institute for Learning and Memory was held on June 3–4, 2009, on Cape Cod. More than 90 researchers attended the two-day event. The retreat included five laboratory research presentations, a highly interactive poster session (12 submissions), and a keynote address by renowned neurobiologist Jeff Lichtman of Harvard University.

Research Initiatives

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 and emotion. Investigating not only the properties of individual cells, cellular clusters, and brain systems but also the functions generated by their communications is 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 multielectrode recording technology, optical and magnetic imaging techniques, and behavioral studies, the center uses an interdisciplinary approach.

The Viral Vector Core Facility was launched in fall 2008 by the Picower Institute in partnership with the McGovern Institute for Brain Research and the support of an anonymous donor. Dr. Rachael Neve, a renowned expert in viral vector research, was appointed as the director. 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 genetically modified mice for sophisticated manipulations of neuronal function. The facility develops genetically modified viruses that can be used to safely deliver genes to neurons. This technology allows research laboratories to answer basic questions about how specific types of neurons contribute to brain function and behavior. Using viruses to introduce into specific classes of neurons genes that make them uniquely sensitive to drugs has the potential not only to greatly advance understanding of the brain but also to provide new treatments in humans for neurologic and psychiatric disorders.

Faculty Research Summaries

The scholarly excellence of the Picower Institute faculty is reflected in distinguished publication records. In the reporting period, Picower Institute faculty published 14 articles in hallmark science journals (*Science*, *Neuron*, *Cell*, and *Nature*) and 46 peer-reviewed publications overall.

Picower Institute faculty research areas are summarized below.

Mark F. Bear's laboratory seeks to understand how experience modifies the brain. It has long been assumed that experience-dependent synaptic plasticity in the visual cortex is confined to a critical early postnatal period. Research by Bear's laboratory has forced a revision of this view. Using behavioral and electrophysiologic approaches, his laboratory found remarkable plasticity in the visual cortex of adult rodents. For example, repeated presentations of visual stimuli greatly increased the cortical response to those stimuli,

a phenomenon that closely resembles perceptual learning. Bear's laboratory went on to show that this increase was specifically due to the delivery of new glutamate receptors to the stimulated synapses—providing the first significant insight into the molecular basis for perceptual learning. In related work, the laboratory has provided the first demonstration that learning induces long-term synaptic potentiation (LTP) in the hippocampus, confirming that learning-induced enhancements partially occluded subsequent LTP in vivo and indicating that learning-induced enhancements and LTP utilize common expression mechanisms. These data provide direct evidence that LTP-like synaptic strengthening occurs naturally in the hippocampus when new information is learned. (This research was selected as one of the 10 breakthroughs of 2006 by the journal *Science*.) Continuing studies are aimed at tracking the duration of these synaptic changes and the effect of their reversal on memory. Other efforts in Bear's laboratory have made extensive use of awake in vivo recordings and two-photon imaging to document the time course of visual cortical plasticity induced by monocular deprivation (an initial deprived-eye depression is followed by potentiation of open-eye responses) and genetic methods to uncover the mechanisms at work in both the temporal and the laminar domain. Findings from Bear's laboratory have described common mechanisms underlying experience-dependent plasticity and the phenomena of LTP and long-term depression in the visual cortex and have added to our understanding of the activity patterns and changes in receptor levels driving both plasticity and metaplasticity in the visual cortex. The laboratory has also described activity changes in the visual cortex related to reward timing and has developed in vivo and in vitro models to study the network and cellular mechanisms involved. Bear's laboratory continues to aggressively study fragile X syndrome (FXS), the most common form of mental retardation and a known genetic cause of autism. Work in Bear's laboratory has established that many aspects of FXS can be corrected by reducing signaling through metabotropic glutamate receptors, a finding with significant therapeutic implications.

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 neurologic 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 pathologic 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 the 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 physiologic 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. They published a paper in *Neuron* demonstrating the first direct neurophysiologic evidence for a moving spotlight of attentional focus during searches of the visual environment. These shifts in the attentional spotlight were synchronized with oscillations in population activity, suggesting a "clocking signal" that regulates attentional shifts. They also recorded neural activity simultaneously in the prefrontal cortex and striatum to examine the role of feedback in learning. They found that neurons in both areas kept track of recent successes and failures. Moreover, these successes and failures influenced the neural activity and behavior: behavioral responses were more often correct and neurons more finely tuned when the previous trial was correct. These results indicate how feedback from the environment helps guide learning and why we often seem to learn more from successes than from failures. These results were also published in *Neuron*.

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* knockout (cpg15 KO) mouse. Overall sensory and motor function, as well as gross brain anatomy and dendritic morphology, were normal in these mice at eight weeks of age. Nevertheless, cpg15 KO mice had difficulty with learning tasks. We 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 (EM) in different subfields of the hippocampus. The lab 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 EM 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 with 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. Proteins that concentrate in synapses and that control synapse structure and function are emerging as strong candidates for causing human brain disorders ranging from autism to Alzheimer's disease. One family of synaptic proteins originally identified by the Sheng lab (the Shank family of scaffold proteins) has recently been genetically linked to autism. A genetically modified mouse made by the Sheng laboratory lacking one of the Shank family proteins has anatomical and behavioral phenotypes reminiscent of the autism spectrum disorder and may prove to be a useful mouse model of the human illness. In another study, a protein kinase (Plk2) was found to be induced by synaptic stimulation and to cause dismantling of synapses and depression of synaptic strength. This negative feedback mechanism, which was abolished if Plk2 function was disrupted, is probably important for the brain to maintain homeostatic balance. The Sheng laboratory discovered that, without Plk2, brain circuits become overactivated and saturated, potentially leading to epilepsy.

Mriganka Sur's laboratory uses cutting-edge technologies for imaging cells and molecules in the intact brain, combined with novel probes, to reveal mechanisms of cortical plasticity and discover the function of cortical cells and circuits. In the past year, his laboratory made two key discoveries that promise to have a significant impact on the understanding and treatment of autism. First, his laboratory pinpointed two genes that cause autism-like symptoms in mice, showing for the first time that multiple, interacting

genetic risk factors may influence the severity of autistic symptoms. The work also indicates that drugs targeting signaling mechanisms between the two interacting genes would be therapeutic for a subset of autism. Second, his laboratory discovered that a key pathway downstream of the *MeCP2* gene—which is mutated in Rett syndrome, a devastating subset of autism and the most common form of autism in girls—influences synaptic maturation and plasticity. Utilizing a mouse model of Rett syndrome, his group showed that a molecule that promotes brain development upregulates this signaling pathway along with key synaptic molecules and partially restores synaptic, circuit, and behavioral function. This molecule is thus a potential therapeutic for Rett syndrome. Together, these discoveries point to an exciting breakthrough in autism research that an understanding of molecular signals that lead from the genes of autism to synaptic function and plasticity would lead to potential treatments for the disorder.

Susumu Tonegawa's laboratory seeks to understand the brain mechanism underlying memory and its disorders. Among the laboratory'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 1 of about 30,000 mouse genes and the protein it creates is knocked out only in a particular type of neuron of a highly restricted part of the brain. By observing the physiologic 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 *N*-methyl-ᴅ-aspartate (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 information as recalling 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). Also widely publicized is a 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. In addition, Tonegawa's laboratory has 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 employed the CA3-TeTX transgenic mouse, in which CA3 output can be specifically and inducibly controlled. Tonegawa's laboratory found that post-training 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 post-run slow-wave sleep or awake quiescent periods in the mutant mice. Collectively, these results suggest that the post-training integrity of the trisynaptic pathway and the ripple-associated reactivation of hippocampal memory engram are crucial for memory consolidation.

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, she explored novel therapeutic approaches to combat cognitive impairment as the consequence of neurodegeneration. Tsai and colleagues reported a remarkable recovery of long-term memories 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. Finally, in collaboration with Christopher Moore at the McGovern Institute for Brain Research, Tsai investigated the role of the fast-spiking parvalbumin (PV) positive interneurons on synchronous firing of excitatory neurons in the cerebral cortex. Using light-sensitive bacteriorhodopsin, channelrhodopsin-2 (ChR2), to drive the activation of PV neurons in the somatosensory cortex, Tsai and Moore show that this leads to induction of gamma oscillations and sharpening of sensory responses. This work provides the first causal evidence for the induction of distinct network activity states by activation of a specific cell type in the brain. As gamma oscillations are frequently disrupted in mental disorders, including schizophrenia and autism, this work provides insight into the mechanisms underlying these diseases.

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 found 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 both in processing memories of the past as well as in imagining future events. Current work seeks to characterize the detailed structure of brain activity as rats navigate and contemplate such mazes, and researchers have 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 is interested in elucidating the molecular mechanisms that mediate activity-dependent modifications of neuronal properties (neural plasticity), which are essential for the immense computational power of the neuronal network for information processing and storage. Dysregulation of neuron excitability and synaptic efficacy is often manifested in neurologic and psychiatric disorders and is thought to underlie some of the cognitive impairment and dysfunction often seen in these diseases. The laboratory aims to study the precise function and interplay of molecular components involved in activity-dependent modification of synaptic efficacy and neuron excitability. Using hippocampal organotypic slice cultures as a model system, researchers manipulate genes in single mature neurons and directly measure the effect of molecular manipulations on electrophysiologic 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. By using this system, the laboratory aims to address three key questions: (1) What is the protein network that conveys the signaling specificity for synaptic plasticity?, (2) How are calcium/calmodulin dynamics regulated during synaptic plasticity?, and (3) What is the contribution of voltage-sensitive conductance to neural plasticity and neuronal encoding? The outcome of these studies will provide targets for pharmacologic interventions for patients with neurodegenerative diseases and psychiatric disorders.

Mark F. Bear
Director
Picower Professor of Neuroscience

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