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, particularly 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 Miller, Picower professor of neuroscience in the Department of Brain and Cognitive Sciences (BCS), was nominated the 2011 Biomed Distinguished Lecturer by the University of Leuven.

Sherman Fairchild professor in neurobiology Matt Wilson (BCS and Biology) was elected a new member of one of the nation's most prestigious honorary societies, the American Academy of Arts and Sciences.

Myriam Heiman, Picower assistant professor of neuroscience in BCS, received a William N. and Bernice E. Bumpus Innovation Award, awarded to early career investigators studying the causes and prevention of Parkinson's disease.

Picower professor of neuroscience Mark Bear (BCS) was given a Pioneer Award for translational research by FRAXA Research Foundation at the 2011 FRAXA Investigators Meeting held September 18–21. He was also recognized with an award for outstanding contributions to the study of metabotropic glutamate receptors at the 7th International mGluR Meeting held October 2–7.

Picower professor of neuroscience Li-Huei Tsai (BCS) and Paul E. Newton professor of neuroscience Mriganka Sur (BCS) were both elected to the US Institute of Medicine of the National Academies in October.

Li-Huei Tsai was the keynote speaker to the 3rd Annual Emerging Scientists Symposium hosted by Research and Education of Memory Impairments and Neurological Disorders (ReMIND).

Li-Huei Tsai delivered the 2012 Elaine Sanders-Bush Lecture on "Restoring memory formation following neurodegeneration-mediated cognitive impairment" in May 2012. She was also elected councilor for the Society for Neuroscience in summer 2011.

Mriganka Sur was appointed director of the newly founded Simons Center for the Social Brain at MIT. An alumnus of Vanderbilt University, he was awarded the 2012 Psychological Sciences at Vanderbilt Distinguished Alumnus Award.

Research Breakthroughs

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

Picower associate professor Elly Nedivi's laboratory (BCS and Biology) found that inhibitory spine and shaft synapses respond differently during normal and altered visual sensory experience, and when the inhibitory synapses and dendritic spines of cortical neurons are rearranged, they are locally clustered, based on sensory input.

Li-Huei Tsai's laboratory identified a brain cell aberration tied to autism. A gene linked to autism spectrum disorders actually alters individual brain cells' ability to process information.

Research from Earl Miller's laboratory suggests a potential explanation for why autistic children focus intently on details, but often seem unable to group things into broad categories.

Mark Bear and his lab colleagues have now shown that tuberous sclerosis, another rare disease characterized by autism and mental retardation, is caused by too little synthesis of those synaptic proteins.

Li-Huei Tsai's laboratory has shown that an enzyme that is overproduced in the brains of patients with Alzheimer's disease creates a blockade that shuts off genes that are necessary to form new memories. Further, by inhibiting that enzyme in mice, the researchers were able to reverse Alzheimer's disease symptoms in mice.

In Picower professor of neuroscience Susumu Tonegawa's laboratory (BCS and Biology), researchers used optogenetics to show that memories really do reside in very specific brain cells, and that simply activating a tiny fraction of brain cells can recall an entire memory.

Personnel

In addition to 11 faculty members, the Picower Institute includes other researchers, students, and technical and administrative support personnel. More than 270 MIT community members participated in Picower Institute activities in AY2012—11 faculty members, 3 visiting scientists/scholars, 55 postdoctoral colleagues, 77 undergraduates, 24 graduate students, 84 research and technical staff, and 17 administrative and service staff.

Items of note during the academic year included:

- Kay Tye, Picower assistant professor of neuroscience started as the newest junior faculty member within the Picower Institute for Learning and Memory (and the Department of Brain and Cognitive Sciences).
- Silvia Da Rosa joined the Picower Institute headquarters team in January as a financial assistant I.

- April London joined the Picower Institute headquarters team in April as a financial assistant II. April brings with her experience as an administrator for the MIT Singapore program.
- Alicia Mackin joined the Picower Institute headquarters team in April as a program administrator overseeing the bequest of the late Jeffry Picower. Alicia brings with her experience as a grants manager at Boston Medical Center.
- Jia Meng joined the Picower Institute headquarters team in March of as a bioinformatician.

Resource Development

Raising the resources to enable the faculty and students in the Picower Institute to carry on their work remains a high priority. This year the Picower Institute received $25 million as a bequest from Jeffry Picower's estate, and an additional $2 million from the JPB Foundation for Picower Institute Innovation Fund. In FY2012, many Picower Institute faculty members gave freely of their time for meetings with donors and potential donors.

The Spring 2012 Picower Institute Symposium on April 18 provided an opportunity to showcase the work of Picower faculty and others on a topic very dear to Mrs. Picower (as well as to others). The "New Insights on Early Life Stress and Mental Health Symposium" was exceptionally well attended throughout the day. A dinner for speakers and donors was held at a private restaurant following the symposium. Subsequently, the JPB Foundation has asked the Picower Institute to submit a proposal for additional funding on this area of research.

Renewed leadership gifts included additional funds in support of a postdoc in Li-Huei Tsai's laboratory. Another repeat donor continues to support the work of Elly Nedivi's work on bipolar disease. The Picower Institute was pleased to receive a $300,000 gift from a foundation to understand the cause and prevention of Parkinson's disease. There were additional gifts from alumni and friends.

Media Recognition

The Picower Institute has attained a distinguished international reputation as a leader in neuroscience research. The scholarly excellence of our faculty is reflected in their distinguished publication records. In AY2012, Picower Institute faculty published 19 articles in hallmark science journals (Science, Neuron, Cell, Nature, Nature Neuroscience, Journal of Neuroscience) and 47 peer-reviewed publications.

The Picower Institute issued 11 MIT press releases in the same time period. Articles appeared in the following major print media: the Boston Globe, F1000, and Science Daily. Picower Institute research breakthroughs were also broadcast via the web on CNN.com, Boston.com, and Dailymail.co.uk, as well as on WBUR, Boston's National Public Radio station.

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 Dr. Eve Marder from Brandeis University, in Waltham, Massachusetts. Her talk, entitled "Post Connectome Analyses of Circuit Dynamics," took place on May 10.

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, colloquia speakers included Dr. Kang Shen of Stanford University, Dr. Rita Balice-Gordon of the University of Pennsylvania, Dr. Steven A. Siegelbaum of Columbia University, Dr. Jonathan Wallis of the University of California, Berkeley, Dr. Pablo Castillo of Einstein College of Medicine, and Dr. BJ Casey of Cornell University.

In 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 not yet published, research with colleagues. The Plastic Lunch series is 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 community was also provided with a new lounge that provides a space to gather, both formally and informally. Throughout the past year the postdoctoral community convened a series of informal talks, educational seminars, and social events.

A monthly Picower Institute faculty lunch, known as the Picower Power Lunch, allows faculty and guest speakers to informally relate recent research findings or present a new idea.

Each year, after the close of the academic year, the Picower Institute hosts an annual retreat for its community. The fifth annual Dana and Betty Fisher Retreat of the Picower Institute for Learning and Memory was held on June 25 and 26, 2012. More than 130 researchers attended the event, held in South Yarmouth, MA. The retreat included 11 laboratory research presentations, a highly interactive poster session (24 submissions), and a keynote address by renowned neurobiologist Howard Eichenbaum of Boston University.

Research Initiatives

The Induced Pluripotent Stem Cell (iPS) Core Facility integrates the various research goals of members of the Picower and McGovern Institutes, and MIT's Department of Brain and Cognitive Sciences (BCS). The various Picower, McGovern, and BCS 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.

The fate of human fibroblast cells can be changed by introducing some genes of interest, such as Octamer-4 (OCT4), Nanog homeobox (NANOG), SRY-related HMG-box gene 2 (SOX2), cMYC proto-oncogene myc (cMYC), and Kruppel-like factor 4 (KLF4) into pluripotent stem cells, which can be called induced pluripotent stem (iPS) cells. These iPS cells resemble embryonic stem cells. Various patient-derived skin primary fibroblast cells are being used to make iPS cells. These patient-specific iPS cells allow researchers to examine a variety of fundamental questions of human disease, which cannot easily be done with embryonic stem (ES) cell technology because ES cells generally don't "know" the health status of an unborn embryo. Therefore, this iPS cell technology creates a powerful research tool that will enable researchers to study disease processes for which they have had only limited access. The iPS cells allow the creation of cell lines that are genetically customized to a patient; thus the issue of immune rejection can be potentially overcome. The iPS cells can be used to screen patient-specific novel therapeutic drug screening and to study the mechanism of multiple neuropsychiatric and neurodegenerative disorders.

Currently, the iPS core facility has produced seven patient-specific iPS cells from patients with schizophrenia, bipolar disease, depression, Rett syndrome, Alzheimer's disease, and healthy control persons' skin fibroblasts. More patient-specific cells (50 and more cell lines) are in the process of being reprogrammed to make iPS cells. Seven people from other laboratories are using the facility to learn how to reprogram cells to make iPS cells and how to differentiate iPS cells into neurons.

Faculty Research Summaries

Li-Huei Tsai's laboratory uses a combination of molecular and cellular, genetic, and behavioral approaches to study neuropathologies that affect cognitive function, such as Alzheimer's disease and psychiatric and developmental disorders. Tsai's laboratory developed an innovative mouse model that exhibited the onset of Alzheimer's symptoms in a fraction of the time previously possible. Using this model, she explored novel therapeutic approaches to combat the cognitive impairment that is 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 non-selective histone deacetylase (HDAC) inhibitors that induce chromatin remodeling. The lab then went on to identify 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 non-selective HDAC inhibitors in facilitating learning and memory. A recent publication has shown that HDAC2 is upregulated in mouse models of Alzheimer's disease as well as in human patients, and that reversing HDAC2 build-up in mice restored normal cognitive functioning.

The Tsai lab has also found that the ectopic expression of cell-cycle genes and activation of the cellular DNA damage response are prominent events preceding neuronal loss. Her laboratory showed that increases in the neurodegeneration-associated p25 protein leads to reduction in the function of histone deacetylase 1 (HDAC1), a protein involved in the maintenance of genome integrity. These observations provide the first evidence for loss of genome integrity in the pathogenesis of neurodegenerative diseases. The Tsai group has also revealed the mechanism by which another HDAC, SIRT1, regulates learning and memory and BDNF/CREB expression by suppressing micro-RNA134 transcription.

Tsai also made major advances in the understanding of the biology of neuropsychiatric disorders and autism. 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. A recent study explored targets of the microRNA miR-137, a risk gene associated with both schizophrenia and autism. Ongoing work is characterizing the neurobiological roles of different candidate psychiatric risk genes. Another publication in 2012 detailed the effect of defects in the autism risk gene TAOK2 on the early development of neurons in the brain.

The modification of synapses by neural activity has been proposed as 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 pre- and post-synaptic activity. Well-studied examples of this type of synaptic plasticity are long-term potentiation and long-term depression. Is it possible to exploit the current understanding of these mechanisms to strengthen brain connections that may have been weakened or impaired by sensory deprivation, disease, or injury? Theoretically motivated research in 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 prior history of synaptic or cellular activity. Studies in 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 NMDA-receptor structure and function. The knowledge gained by these studies suggests ways in which recovery of function can be promoted that are now being tested in the Bear lab.

Myriad mechanisms have been suggested to account for the full richness of visual cortical plasticity. In collaboration with Mriganka Sur's laboratory, researchers in

Mark Bear's laboratory found that 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 visual cortex is that, by adolescence, an excitatory synapse is rendered essentially immutable by experience or deprivation if Arc is not expressed in its postsynaptic target. Despite this profound defect in acquired properties, the innate organization and levels of visual responsiveness appear to be normal in Arc-knockout mice. It appears that a requirement for Arc is a bright line that separates the contributions of "nurture" (those dependent on the quality of sensory experience) from "nature" (those dependent on genetic instructions alone) on the development of glutamatergic synaptic connections in the cortex.

Fragile X syndrome is the leading inherited cause of mental retardation and autism. Recent advances in mechanistic understanding of the disease have led to the 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 seen if mGluR5 antagonists or related approaches will succeed in humans with fragile X, the progress in fragile X 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.

Dr. Myriam Heiman's laboratory uses molecular, cellular, and behavioral approaches to study the molecular mechanisms underlying neurodegeneration. Among the tools the laboratory uses are transgenic mice that allow molecular studies of individual nerve cell populations. The group's research has focused on the study of what intrinsic and disease-induced differences characterize nerve cells that are more or less vulnerable in neurodegenerative diseases of the basal ganglia. Recent work has identified candidate vulnerability factors that appear to enhance the toxicity of mutated Huntingtin protein, which is involved in the pathophysiology of Huntington's disease.

Troy Littleton is the Picower Professor of Neuroscience in the Departments of Biology and Brain and Cognitive Sciences. The focus of his laboratory's work is to understand the mechanisms by which neurons form synaptic connections, how synapses transmit information, and how synapses change during learning and memory. To complement this basic research in neuroscience, Littleton also studies how alterations in neuronal signaling underlie several neurological 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. A major goal for the next decade of neuroscience research is determining how proteins specify the distinctive signaling properties of neurons and enable them to interconnect into computational circuits that dictate behavior. Despite the dramatic differences in complexity between Drosophila and humans, genomic analysis has confirmed that key neuronal proteins and the functional mechanisms they govern are remarkably similar. Given this, researchers in the Littleton laboratory are attempting to elucidate the mechanisms underlying synapse formation, function, and plasticity using Drosophila as a model system. By characterizing how neurons integrate synaptic signals

and modulate synaptic growth and strength, researchers hope to bridge the gap between molecular components of the synapse and the physiological responses they mediate.

The overarching goal of Earl Miller's laboratory is to understand cognitive functions in a broader context as a product of interactions between networks and circuits of neurons, brain areas, and systems. The Miller lab 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.

Elly Nedivi's 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 activity-regulated genes that affect neuronal structure, researchers in the Nedivi lab started a long-standing collaboration with Peter So's lab in the Department of Mechanical Engineering to develop multiphoton microscopy for large-volume, high-resolution imaging of dendritic arbor and synaptic structural dynamics in vivo. Nedivi lab researchers were the first to reveal interneurons as capable of dendritic arbor remodeling in the adult.

Once interneurons were recognized as key players in activity-dependent circuit plasticity, a major obstacle to addressing questions regarding inhibitory synapse plasticity (as well as how it may be coordinated with excitatory inputs at the dendritic level) has been the inability to visualize inhibitory synapses in vivo. Recently, again in collaboration with Dr. So, Nedivi lab researchers expanded their high-resolution, large-volume imaging capabilities with incorporation of two-color multiphoton microscopy to simultaneously monitor both inhibitory synapse and dendritic spine remodeling across the entire dendritic arbor of cortical L2/3 pyramidal neurons in vivo during normal and altered sensory experience. This has allowed researchers to address, for the first time, fundamental questions about the interplay between excitatory and inhibitory synaptic transmission during normal adult brain function as well as experience-dependent plasticity.

These studies led to several significant findings:

- Inhibitory synapses on dendritic shafts and spines differ in their distribution across the arbor, consistent with different roles in dendritic integration.
- These two inhibitory synapse populations also display distinct temporal responses to visual deprivation, suggesting different roles in early versus sustained phases of experience-dependent plasticity.
- Finally, and most significant, the rearrangements of inhibitory synapses and dendritic spines are locally clustered, mainly within 10 μm of each other, which is the spatial range of local intracellular signaling mechanisms, and the extent of clustering is influenced by experience.

Mriganka Sur's laboratory developed a new technological platform for light-based circuit interrogation in the intact cortex that allowed researchers to activate single neurons and synapses and record the effects in connected neurons within a functioning circuit. Combined with genetically engineered mice, the laboratory used this platform to reveal new computational roles for inhibitory neuron classes in the visual cortex: soma-targeting parvalbumin-expressing inhibitory neurons divide target cell responses and control response gain, whereas dendrite-targeting somatostatin-expressing inhibitory neurons subtract from target cell responses and control response selectivity. Because inhibition is profoundly important for a wide range of brain functions, these findings provide a crucial conceptual framework for understanding cortical circuits that underlie normal and abnormal information processing. In other findings, Sur's laboratory found that cholinergic inputs influence long-term changes in cortical circuits through astrocytes, thereby pointing to a novel but fundamental mechanism of cortical wiring and plasticity.

Susumu Tonegawa's laboratory continues to seek to decipher the brain mechanisms underlying memory and its disorders. During the past year, Tonegawa's laboratory made the following discoveries.

Pattern Completion and Pattern Separation. Previous results with dentate-gyrus (DG) granule cell (GC)–restricted NMDA receptor knockout mice provided strong support for the model in which the entorhinal cortex (EC) layer II to DG to CA3 pathway was implicated in pattern separation. However, these studies did not consider the heterogeneity of the DG GCs. About 95% of these cells are generated during early development and do not divide thereafter but about 5% of GCs originate from resident progenitor cells that generate these cells throughout the animal's life. These adult-born GCs are integrated into the preexisting TSP and are particularly active during the first several weeks, after which they become indistinguishable from less active, developmentally born GCs. Researchers from Tonegawa's laboratory explored the function of DG GCs further by developing a new genetic intervention method that permits the blockade of information flow from one type of cells to another by manipulating tetanus toxin, which can inactivate a presynaptic protein called VAMP2 that is essential for the neurotransmitter release. This triple transgenic mouse technology (dubbed the DICE-K method), incorporating both the Cre-loxP system and the tetracycline transactivator system, allows a inducible and reversible inhibition of synaptic transmission by a particular type of presynaptic cells.

Researchers applied this DICE-K method to old GCs that had been generated during both the developmental and adult periods and generated a mouse in which mossy fiber (MF) input from these GCs is robustly inhibited, whereas MF input from a substantial portion of young (three- to four-week-old) GCs is spared. In these mutant mice, the ability to acquire memories that facilitate discrimination of similar contexts or spaces was unimpaired or even enhanced compared with control mice. These behavioral data were supported by a normal rate of remapping in CA3 and CA1 across similar local environments. In contrast, mutant mice were impaired in rapidly recalling previously acquired contextual and spatial memories, specifically with partial recall cues. When the young GCs were removed from the mutants by X-ray irradiation, the contextual

discrimination capability was reduced. Overall, these data indicate that old GCs do not play a critical role in pattern separation between similar environments but are required for attaining a normal level of rapid pattern completion. These data force major changes in our understanding of the entorhinal–hippocampal network in pattern separation and completion [Nakashiba, T., et al., *Cell* 149: 188 (2012)].

Temporal Association Memory. Another characteristic feature of an episodic memory is an association of temporally discontinuous elements (temporal association memory). The neural circuits subserving these associations have remained unknown. Researchers from this laboratory hypothesized that the "persistent activity" observed in vitro in EC may contribute to this phenomenon through its layer III input to the hippocampus along the monosynaptic pathway (MSP). To test this hypothesis, they created a mouse in which the output of EC layer III cells into the hippocampus is inducibly and reversibly blockable while keeping the TSP intact.

These mutant mice were normal in the acquisition, recall, and consolidation of spatial reference memory, but exhibited significant impairments in three hippocampal-dependent temporal association memory tasks, each requiring the association of two or more elements that appear 15 to 30 seconds apart. These tasks were a water maze version of the delayed matching-to-place task, a delayed non-matching-to-place version of the T-maze task, and trace fear conditioning. Additionally, it was demonstrated that the TFC deficit is specific to the blockade of MSP; another triple transgenic mouse in which the alternative hippocampal loop, namely TSP, is blocked at the CA3–CA1 synapses, was normal in this task. Researchers also showed that it is during the trace conditioning phase, rather than the recall phase, that the EC layer III input plays a crucial role. Further, bilateral injections of known antagonists of persistent activity into the dorsal ECs of control mice impaired trisynaptic pathway. The overall results indicate a critical role of MSP in temporal association memory [Suh, J., et al., *Science* 334: 1415 (2011)].

"Preplay" for Memory Encoding. During spatial exploration, hippocampal neurons show a sequential firing pattern in which individual neurons fire specifically at particular locations along the animal's trajectory (place cells). According to the dominant model of hippocampal cell assembly activity, place-cell firing order is established for the first time during exploration, to encode the spatial experience, and is subsequently replayed during rest or slow-wave sleep to consolidate the encoded experience. However, when an animal starts an exploration of a new space, the hippocampus is not a blank slate. It is composed of numerous cellular assemblies that reflect myriad past experiences. A question then arises as to whether some of the preexisting place-cell sequence fragments could be reused during the exploration of the new space, perhaps to accelerate encoding. To test this hypothesis, researchers recorded from the CA1 area of mice that were resting or sleeping in a high-walled box with no prior experience on any linear track. The animals were then transferred to a novel isolated linear track that was in the same room and the recording continued during de novo formation of place cells. Researchers found that in 16% of spiking events identified during sleep or rest in the sleep box, neuronal firing sequences were correlated with the place-cell sequences observed during the subsequent first run session on the novel track. They call this phenomenon "preplay" to contrast it with replay. These results suggest that internal

neuronal dynamics during rest or sleep organize hippocampal cellular assemblies into temporal sequences that contribute to the encoding of a related novel experience occurring in the future [Dragoi, G. and Tonegawa, S., *Nature* 469: 397 (2011)].

A Clustered Plasticity for Cellular Consolidation of Memory. Encoding is thought to be followed by changes in synaptic weights and neuronal excitability as the neural substrate for the storage of memory engrams. Studies on the Schaffer collateral-CA1 synapses have led to the synaptic tagging and protein capture (STC) model. According to this model, the protein synthesis-dependent LTP (L-LTP) induced at some synapses facilitate L-LTP expression at other synapses receiving stimulation too weak to induce L-LTP by itself. However, these past studies measured the average response of a population of unidentified stimulated synapses and could not determine the spatial limits over which STC can occur or the temporal dynamics of STC at individual stimulated spines. Using glutamate uncaging and two-photon microscopy, researchers in Tonegawa's laboratory demonstrated that the efficacy of the STC decreases with increasing time between stimulations, with increasing distance between stimulated spines, and when the spines are on different dendritic branches. Additionally, L-LTP formation is itself biased toward occurring on spines within a branch. These data support the clustered plasticity hypothesis, which states that such spatial limits lead to stable engram formation, preferentially at synapses clustered within dendritic branches rather than dispersed throughout the dendritic arbor. Thus, dendritic branches, rather than individual synapses, are the primary functional units for cellular consolidation of long-term memory in the hippocampus [Govindarajan, A., et al., *Neuron* 69: 132 (2011)].

Imaging and Manipulating Memory Engram-bearing Cells. A specific memory is thought to be encoded by a sparse population of neurons. These neurons can be tagged during learning for subsequent identification and manipulation. In addition, memories can be artificially allocated to a subset of neurons and erased by the ablation or inactivation of these neurons, demonstrating their necessity for memory expression. However, a critical question of sufficiency remains: can one elicit the behavioral output of a memory by directly reactivating a population of neurons that was naturally active during learning?

Researchers demonstrated that optogenetic activation of hippocampal neurons labeled during fear conditioning is sufficient to induce freezing behavior. In the experimental group, we labeled a population of hippocampal dentate gyrus neurons active during fear learning with channelrhodopsin-2 (ChR2) and later optically reactivated these neurons in a different context. The animals showed increased freezing as an indication of fear memory recall only upon light stimulation. This freezing was not detected in non-fear–conditioned animals expressing ChR2 in a similar number of cells, nor in fear-conditioned animals with cells labeled by EYFP instead of ChR2. Activation of cells labeled in a context not associated with fear did not evoke freezing in animals previously fear-conditioned in a different context, suggesting that light-induced fear memory recall is context-specific. Together, these findings indicate that activation of a sparse but specific ensemble of hippocampal neurons that contribute to a memory engram is sufficient for memory recall. Moreover, this experimental approach

should permit the cellular mapping of memory formation and recall not only in the hippocampus but also in other brain areas that participate in memory processes [Liu, X., et al., *Nature* 484: 381 (2012)].

Work in Matthew 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 on 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; it is also consistent with recent evidence in humans that suggests that the hippocampus is involved in both 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. The ability to reconstruct the content of this activity has been successfully demonstrated, providing a potential window into the process of thought itself.

The laboratory of Picower assistant professor of neuroscience Weifeng Xu (BCS) 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 for 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. Two lines of research are conducted in the laboratory.

Using the molecular replacement approach, Xu's laboratory has discovered that the members of the postsynaptic scaffold PSD-MAGUKs family of proteins have overlapping yet distinct effects on basic properties of synaptic transmission. This includes active synapse numbers, unitary synaptic strength, and activity-dependent regulation, suggesting an elaborated regulation of synaptic function orchestrated via PSD-MAGUK family proteins. This functional diversity may underlie their specific functional significance during development and experience-dependent plasticity.

Calcium (Ca) and Ca-binding protein calmodulin (CaM) are important messengers mediating electrical signals to cellular signaling. Researchers in Xu's laboratory have discovered that the levels of an apo-CaM binding protein (neurogranin) can be rapidly regulated by experience and neuronal activity, providing an experience-dependent regulation of Ca signaling in neurons in a very short time. Bidirectional manipulation of neurogranin levels using virus-mediated knockdown and overexpression lead to bidirectional change of neuronal excitability, suggesting that this pathway may contribute to activity-dependent regulation and modulation of neuronal network activity. Ongoing research aims to further examine the functional implication of this rapid experience-dependent regulation of neurogranin levels in learning and in synaptic plasticity. The outcome of these studies will provide targets for pharmacological interventions for patients with neurodegenerative diseases and psychiatric disorders.

Since Dr. Kay Tye's arrival at the Picower Institute in January 2012, she has been working to use "reverse translational" approaches to identify the circuit and synaptic mechanisms underlying emotional processing and motivated behaviors in both health and disease in rodent models. The long-term objective of the laboratory is to identify common circuit perturbations that may underlie comorbidity between psychiatric disease states such as addiction, anxiety, and depression. To do this, Tye's laboratory employs an interdisciplinary approach that integrates electrophysiological, optogenetic, pharmacological, and imaging techniques to study the neural bases of behavior. This year, the laboratory has already begun to collect preliminary data identifying novel circuit dynamics involved in anxiety-related behaviors.

Li-Huei Tsai
Director
Picower Professor of Neuroscience