Picower Center for Learning and Memory

The primary mission of the Picower Center for Learning and Memory is to create a world-class focus for research and education in neuroscience. Since learning and memory are central to human behavior, the center's research aims to understand the mechanisms underlying these cognitive functions at the molecular, cellular, and brain circuit levels. The center's research also extends to other higher order cognitive phenomena intimately associated with learning and memory, such as attention, decision making, and consciousness. The development of the brain in early life depends on interactions between the organ's innate genetic program and stimuli from the environment. Therefore, the Picower Center's research also seeks to understand how a child's brain develops and how the environment affects it.

Major Research Breakthroughs

- A discovery in Mark Bear's laboratory that blocks or dampens the function of a metabotropic glutamate receptor in the brain may lighten or cure mental retardation, autism, and Alzheimer's disease.
- A discovery made in Earl Miller's laboratory indicated that the basal ganglia (which are important in Parkinson's disease) may begin to generate "guesses" about the correct course of action early in learning, whereas the more executive prefrontal cortex waits for more evidence before it lets the monkey's behavior change.
- A discovery was made in Elly Nedivi's laboratory of the first cell survival factor (called CPG15) in immature neurons that may protect specific subpopulations of neurons during brain development.
- A discovery was made in Susumu Tonegawa's laboratory of a specific gene and its protein product (calcineurin) whose genetic variation (or mutation) is associated with schizophrenia, providing molecular targets for the development of novel antipsychotic drugs.
- A discovery was made in Matthew Wilson's laboratory that neuronal activities that represent experienced sequences of events are repeated (replayed) in the same sequence during slow-wave sleep, indicating sleep may play a crucial role in establishing long-term memories.

New Building and Faculty Hiring

We have watched the construction of our new building (at the intersection of Albany and Vassar Streets) with pride and excitement and enthusiasm for the opportunities that will come to fruition with its completion. The building is slated to open in fall 2005 and will provide space for our 11 current faculty and for 2 additional faculty members, for whom searches have begun. One opening is for an investigator in the area of disease research and the other is for a primate researcher.

Public Relations

During the summer of 2003 , the Picower Center published its first brochure, which has been widely distributed for informational and fund-raising purposes. We are proud to report that this publication won a Council for the Advancement and Support of Education (CASE) Gold Award in the category of development publications. Also, our newly designed and organized website went live in November 2003 and can be viewed at http://web.mit.edu/picowercenter/.

Promotions

Matthew Wilson was promoted to full professor and Troy Littleton was promoted to associate professor.

Awards

Mark Bear was elected fellow to two prestigious organizations: the American Association for the Advancement of Science and the American Academy of Arts and Sciences.

Carlos Lois was named Ellison Medical Foundation scholar.

Mriganka Sur was appointed to the Advisory Council of the National Eye Institute.

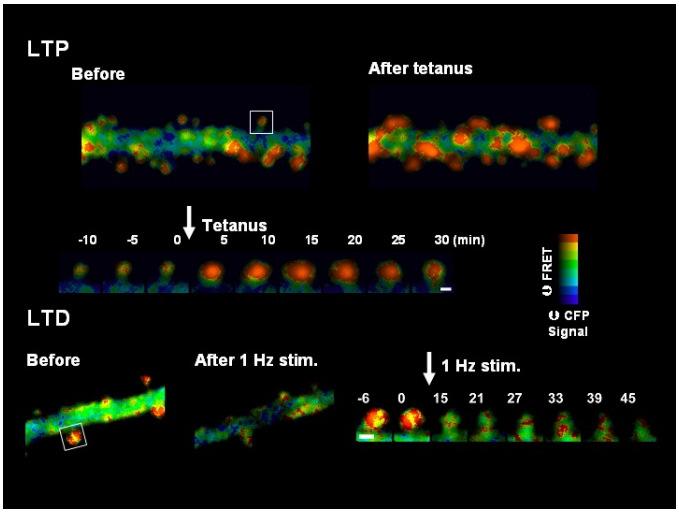
Susumu Tonegawa received an honorary degree from his alma mater, Kyoto University.

Our Picower Center brochure, published in August 2003, won a CASE Circle of Excellence Gold Award in the category of development publications and will be on display at the CASE International Assembly in July 2004.

Research Highlights

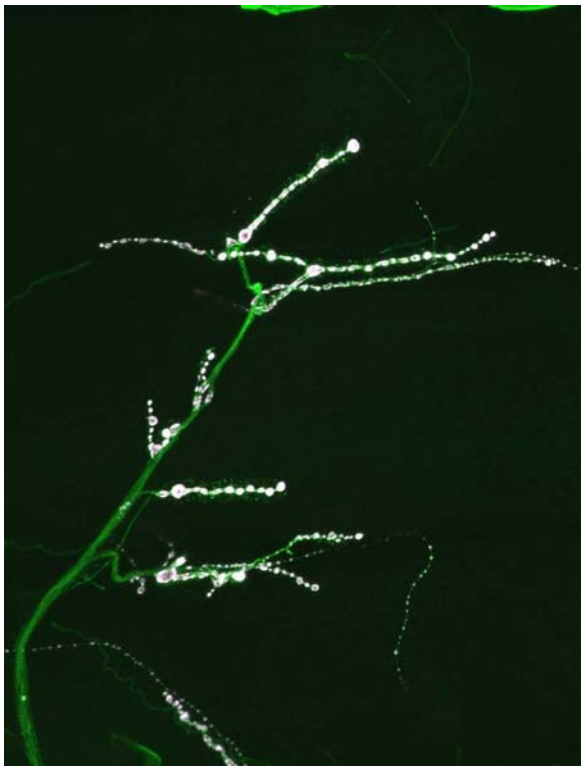
The Bear laboratory seeks to understand how connections among brain cells in the hippocampus—the brain region critical for memory formation—and in the visual cortex are modified by signals from the outside world. The laboratory's recent discovery on how synapses are weakened promises to shed light on disorders such as mental retardation, autism, and Alzheimer's disease. By blocking a single brain chemical—a metabotropic glutamate receptor—many of the psychiatric and neurological disabilities associated with a leading cause of mental retardation could be treated. The Bear laboratory also discovered a key molecular mechanism underlying plasticity in the visual cortex, showing that the striking loss of vision in an eye temporarily deprived of normal vision during a critical postnatal period is a consequence of residual retinal afferent activity that fails to correlate with evoked postsynaptic responses in the visual cortex. The deprivation induces a series of events that cause the unused synapses to be eliminated.

By exploring the connections among brain cells in the memory-forming part of the brain, the hippocampus, Hayashi's laboratory builds understanding of how memory is formed at the molecular level. Using electrophysiology, optical imaging, and molecular biology techniques, his laboratory observes the dynamics of individual proteins in single neuron-to-neuron connections. The Hayashi laboratory's ongoing projects focus on the molecular biology of excitatory synaptic transmission, including an exploration of whether a dysfunction of an NMDA receptor causes motoneuron disease such as amyotrophic lateral sclerosis, also known as Lou Gehrig's disease.



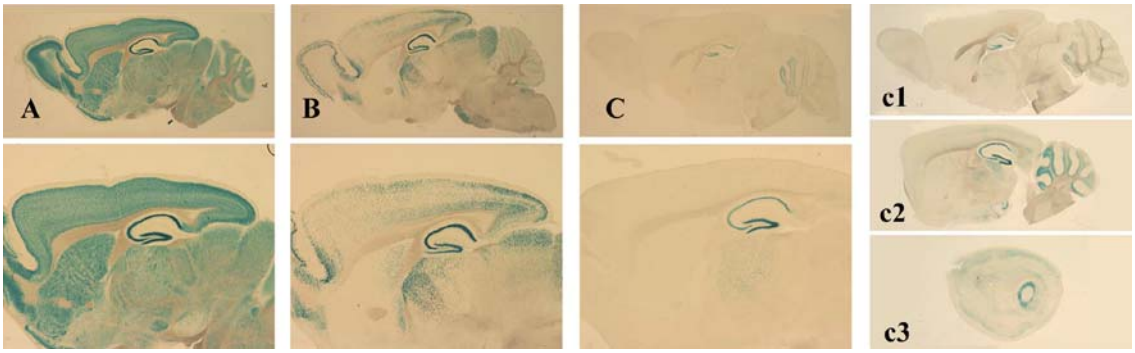
An optical detection system indicates that the protein actin in actively involved in learning and forgetting.

Using the fruit fly *Drosophila* as a model, Littleton's laboratory studies the alterations in neuron-to-neuron signaling and connection that underlie epilepsy, Huntington's disease, Alzheimer's disease, and other genetically complex disorders. The laboratory also looks at how the connections among neurons change during learning and memory. The Littleton laboratory seeks to elucidate the molecular mechanisms underlying synapse formation, function, and plasticity by combining molecular biology, protein biochemistry, electrophysiology, and imaging approaches with genetics. They have identified many previously unsuspected gene candidates in the fly brain for activity-dependent modulation of neuronal function. The lab is now determining how these genes contribute to cellular forms of behavioral plasticity. Together, these approaches should greatly expand the understanding of the basic mechanisms of synapse function and plasticity, as well as provide insights into expression changes that allow synaptic ensembles to store information through changes in neuronal connectivity and function.



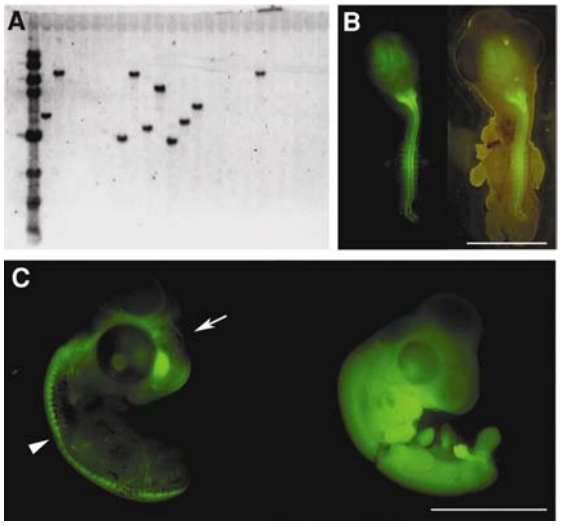
Expression of Synaptotagmin I at Drosophila *neuromuscular junctions.*

Guosong Liu's laboratory aims to understand how neurons in our brains physically form connections, why they choose to make certain connections and how those connections—our memories—can be so precisely maintained. Through an advanced technique that allows the manipulation of single brain connections, they hope to create models for how memory might be improved and disease alleviated. By studying the principles that guide the formation of functional neural circuits, Liu's laboratory found that excitatory and inhibitory synapses are organized in an ordered fashion on a neuron's dendritic tree to maintain a local balance of excitation and inhibition. Surprisingly, this balance of excitation and inhibition is essential for plasticity of synapses. These findings may further the understanding of how synaptic plasticity is regulated in vivo.



LacZ expression in the brain of animals carrying single copies of enhancer detector probes. The top and bottom images correspond to different magnification views of the same brains.

Using genetic technologies that allow researchers to manipulate the birth, death, and formation of newly generated neurons, Carlos Lois's laboratory explores neurogenesis—the surprising ability of certain species to grow new brain cells in adulthood and integrate them into existing brain circuits. A long-term goal is to harness this regenerative ability to correct neurological defects from injury or disease. Retroviruses have become one of the preferred viral-based gene delivery vehicles because of their ability to permanently integrate into the genome of target cells. Recently, the Lois laboratory demonstrated that lentiviruses (another family member in the retroviridae class) are not subject to the developmental silencing observed with oncoretroviruses. Lentiviral-based vectors can be used to express genes in specific tissues or cell types when engineered with tissue-specific promoters. Because of these properties, lentiviral vectors could allow for the genetic modification of species that until now have not worked well with transgenic approaches, such as birds or primates.



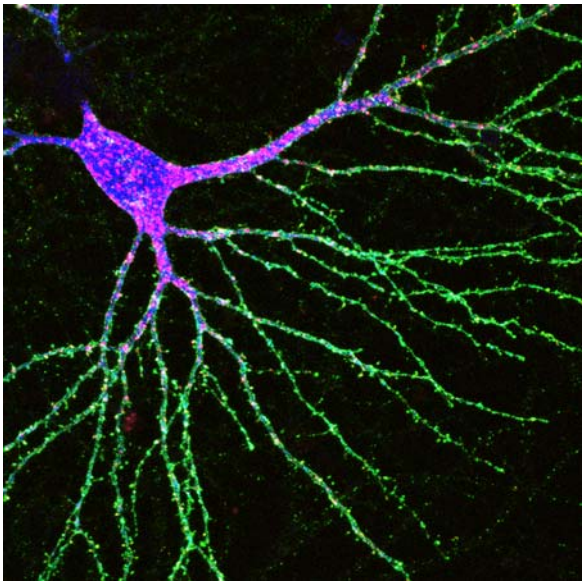
Southern blot analysis of genomic DNA from progeny of Hsyn mosaic founders.

Earl Miller's laboratory is one of a few in the world studying the prefrontal cortex,

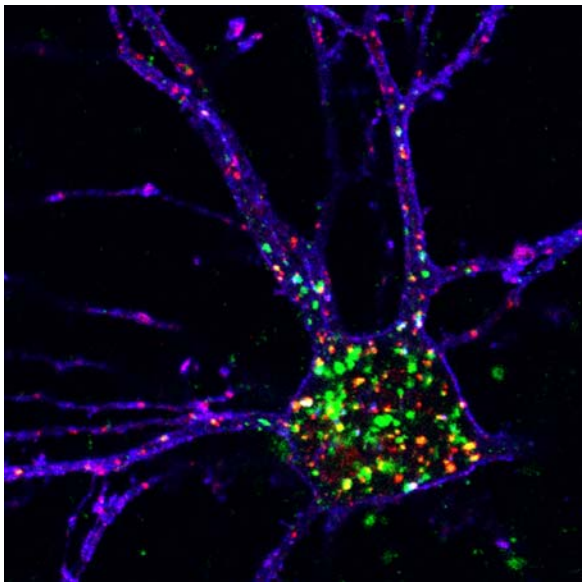
home of the brain's high-level "executive" functions such as paying attention, recalling memories, categorizing objects, and piecing together the information it takes to achieve a complex goal and manage daily life. The laboratory links sophisticated behavioral studies with techniques for analyzing the activity of groups of neurons with the goal of understanding schizophrenia, attention deficit disorder, obsessive-compulsive disorder, and others. The Miller laboratory's studies have provided insight into how the prefrontal cortex and related brain areas acquire the knowledge about the high-level, abstract categories, concepts, and rules needed to guide intelligent, goal-directed behavior. These findings have provided a foundation upon which to construct more detailed, mechanistic accounts of how executive control is implemented in the brain. The Miller laboratory has made key discoveries about how and where concepts such as "number," "cat and dog," "same," and "different" are represented in the brain. They found that their representation shares fundamental properties with lower-level information, such as brightness. This suggests a continuum between lower- and higher-level brain functions and helps resolve one of the oldest and most fundamental debates in cognitive science. The laboratory also has provided key information on how the brain pieces together information about ongoing actions and their consequences.

Using molecular biology techniques, Nedivi's laboratory pinpoints which of the brain's genes are involved in making memories and details how they work. This fundamental understanding may eventually help scientists design highly targeted drugs for disorders such as Alzheimer's disease. Nedivi's laboratory is working on characterizing CPG15, a gene isolated in a genetic screen that may play a role in synaptic plasticity. The gene encodes a small protein, CPG15, present in vertebrate species. The lab has shown that the soluble, secreted form of CPG15 is expressed in regions that are undergoing rapid proliferation and apoptosis in the embryonic brain. CPG15 is the first identified survival factor expressed by undifferentiated neurons, and it may provide a selective force for the protection of specific neuronal subpopulations during morphogenesis of the mammalian forebrain.

The Sheng laboratory is interested in the molecular mechanisms by which synapses in the brain change their strength and connectivity in response to experience. In both the developing and mature brain, there is a regulated balance between elimination of poorly used synapses and the formation of new connections between neurons. The molecular mechanisms underlying these processes are not well understood. During the past year, the Sheng lab has discovered a novel way to eliminate synapses, which involves an activity-induced protein kinase and the degradation of specific synaptic proteins by the ubiquitin-proteasome system. Weakening of synapses can occur by the



NMDA-induced internalization of heteromeric GluR2/3 receptors in hippocampal neuron.



Immunofluorescence image of neuron.

removal of postsynaptic glutamate receptors (AMPA receptors) from the surface membrane into intracellular compartments. The rules that govern the sorting of internalized AMPA back to the surface (recycling) or to lysosomes for protein degradation have been determined.

The Sur laboratory studies mechanisms of development and plasticity in the cerebral cortex. In particular, the laboratory seeks to understand how patterns of activity lead to functional changes in synapses and structural changes in neurons in the developing and adult visual cortex. Mechanisms of brain development lead naturally to the study of developmental disorders of the brain. The Sur laboratory has started to examine the causes of autism by focusing on the genes and molecules responsible for the regional parcellation of the cerebral cortex into discrete processing areas and for synaptic plasticity in these areas; both of these features are implicated in autism. In the past year, the laboratory has also made several important advances in discovering the mechanisms and consequences of brain wiring. As a model for brain development early in life, the lab rewires the brain, inducing projections from the eye to areas outside the visual pathway such as the auditory thalamus. This rewiring profoundly alters neuronal networks and connectivity; the lab has now shown that rewired projections are able to mediate behavioral learning. In the developing visual cortex, the lab has developed tools for high-resolution imaging of single synapses and terminals and shown how neurons in the intact brain dynamically change their contacts as they develop, due primarily to the influence of electrical activity and homeostatic properties of neurons. Finally, in the adult visual cortex, the lab has shown that neurons in the earliest cortical areas in behaving monkeys are able to alter their responses dynamically based on integrating bottom-up visual signals with top-down cognitive signals. The basis for these changes is again a combination of extrinsic and intrinsic influences that drive synaptic plasticity and function in cortical neurons and networks.

Learning and memory are vital for day-to-day living, from finding our way home to playing tennis to making a cohesive speech. Tonegawa's laboratory seeks to understand the brain mechanism underlying memory and its disorders. Among its major discoveries is identifying a protein and neuronal circuitry 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 Alzheimer's disease. Tonegawa's laboratory combines the cutting-edge technologies of genetic engineering, electrophysiology, and behavioral methods. Using a new genetic technology they developed, Tonegawa's research team created mouse strains in which only one 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 physiological and behavioral deficits of these mice, the

Tonegawa laboratory, in collaboration with Matthew 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 one-time experiences and to recall the details of the memory previously formed with scant information as cues. Tonegawa's laboratory also knocked out a gene for the enzyme calcineurin only in the front part of the brain. This mouse strain displayed a number of behavioral deficits shared by human schizophrenia patients. Tonegawa and collaborators showed for the first time that variation in a human calcineurin gene is associated with schizophrenia. This is the first study that uses animals demonstrating an array of symptoms observed in schizophrenia patients to identify specific genes that predispose people to the disease. The work provides novel molecular targets for the development of new therapeutic and diagnostic methods for schizophrenia and possibly for related psychiatric diseases such as bipolar disease and autism.

Using techniques that make it possible to measure the responses and interactions of large groups of neurons, the Wilson laboratory is studying how memories of personal experience are formed and used. This effort has led to the study of sleep and the dreaming life of rats, yielding surprising insights into the relationship between dreams and memory. Wilson's lab, in collaboration with the Tonegawa laboratory, demonstrated for the first time the role of circuits within the hippocampal area CA3 in mice in the formation of memories of novel events. These findings have implications for the formation of human memories. The Wilson laboratory focuses on the role of the hippocampus and its interactions with the neocortex during sleep and waking states in the formation and maintenance of memory in the mammalian nervous system. In a study that increases understanding of the role of sleep in establishing long-term memories, the laboratory also has demonstrated the replay of memories for sequences of events during slow-wave sleep.

Susumu Tonegawa
Director
Picower Professor of Biology and Neuroscience

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