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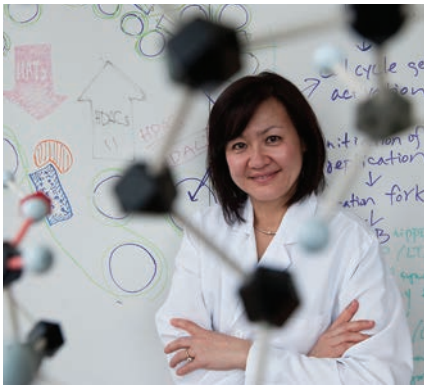
Neuroscience News

Fall 2012

THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY



Li-Huei Tsai

Director, Picower Institute for Learning and Memory

Photo / Len Rubenstein

FROM THE DIRECTOR

LI-HUEI TSAI

The Picower Institute's 10th Anniversary was a perfect occasion for us to host a full day symposium on November 6, 2012 and to bring together some of the best minds in neuroscience. I hope you will enjoy reading about their fascinating research in the following pages.

For us, the anniversary is an occasion for reflecting on our accomplishments of the past ten years, and on the challenges we will continue to tackle in the next decade. Since its inception, the institute has striven to promote great scientific achievements and to attract the finest talent to our laboratories. Scientifically, we have gained new insights into how we learn, how memory works, and the mechanisms of cognition in general. These achievements have only been possible because of the multidisciplinary approach of our investigators as we elucidate different pieces of the very complex puzzle that is the brain.

We have also been using these insights to make important contributions to the understanding of the neurological disorders that affect so much of the world's population. For example, our labs are applying their expertise in the role of experience in the synaptic plasticity of the cerebral cortex and hippocampus, and during development to the study of Fragile X syndrome, Autism, Rhett Syndrome, Alzheimer's disease, and anxiety and depression.

The institute's growing reputation is enabling us to attract phenomenal new talent. In the past few years, we have welcomed three excellent junior faculty, Myriam Heiman, Weifeng Xu, and Kay Tye. Their contributions will help ensure that the next ten years will be even better than the last.

No reflection on where we have been and where we are going is complete without acknowledging the advantage of our location at MIT, at the nexus of technology development. More than any other field in biology, neuroscience depends on technological innovation to make the otherwise hidden organ deep inside our skull accessible to our explorations. We are privileged to be able to work closely with experts in so many fields at MIT, and it is these collaborations that will help us meet the challenges of the future.

COVER:
Picower 10th Anniversary Logo

Picower Institute 10th Anniversary Symposium

Founded in 2002, the Picower Institute for Learning and Memory embraces a highly collaborative, cross-disciplinary approach that addresses every level of brain function from molecules to synapses, neural circuits to behavior. In the past decade, neuroscientists here and elsewhere have developed new technologies and methods for exploring how we learn, remember, think, and behave. Some of the top researchers in the field joined the 10th Anniversary celebration and presented their exciting new work at the symposium on November 6, 2012.

Marc Kastner, Dean of the MIT School of Science, opened the symposium by praising the great research that PILM is undertaking to understand the fundamental science of how the brain works, while looking for opportunities to use this understanding to provide therapies for brain disorders. He commended the vision of founding director, Susumu Tonegawa, for creating a group of great scientists focused on the understanding of learning and memory, the leadership of Mark Bear in convincing Barbara and Jeffry Picower to provide additional funding for high-risk/high-payoff research, and the inspiration of Li-Huei Tsai for increasing the focus on brain disorders.

Using Fixed Circuits To Build Flexible Behaviors

Cornelia Bargmann (Rockefeller University)

Cornelia Bargmann asks: Which aspects of behavior are defined by fixed genetic and developmental programs? How does the brain generate flexible responses to the environment based on context and experience? The nematode Caenorhabditis elegans has a small, genetically hard-wired nervous system, yet its preferences for odors, food sources, and other animals vary based on environmental conditions, internal modulatory states, and genetic variation. She described how variable inputs converge on common neuronal circuits that coordinate behavior.

Mapping motivation: Optical deconstruction of fully assembled biological systems

Karl Deisseroth, MD, PhD (Stanford University)

One manifestation of depression is a decrease in motivation and an increase in hopelessness. Motivation emanates from the prefrontal cortex (PFC), but where does it go from there? Deisseroth's lab used optogenetics, a technology he developed in 2005 to precisely control neurons with pulses of light, to selectively activate PFC neurons projecting to different regions in the brainstem in rats. They could dial up and down the animal's motivation by stimulating different pathways. Stimulating the pathway between PFC and the dorsal raphe nucleus (which is rich in serotonin) increased the animal's efforts, while stimulating that to the lateral habenula (already implicated in depression) decreased it. As a practicing psychiatrist, Deisseroth finds that a deeper understanding how motivation works can help patients seeking to understand their troubling symptoms.

Decoding Neuronal Heterogeneity: Molecular Profiling in Neurodegenerative Disease Models

Myriam Heiman (Picower Institute at MIT)

The vast cellular heterogeneity of the mammalian brain has hampered efforts to understand the normal properties of specific nerve cell types, as well as to understand how these cell types are altered in diseased states. In addition, this cellular heterogeneity has also hampered efforts to understand the mechanism of action of therapeutics used to treat neurodegenerative and psychiatric diseases. In her talk, Dr. Heiman described the development of new molecular genetic techniques that can overcome problems caused by this cellular heterogeneity, and described the application of these techniques to the study of Huntington's disease and Parkinson's disease.

Sleep and amyloid-β: Their reciprocal relationship in regard to Alzheimer's disease

David M. Holtzman, MD (Washington University School of Medicine)

Neuronal activity directly regulates the levels of the amyloid-β (Aβ) peptide in the brain, which is implicated in the pathogenesis of Alzheimer's disease (AD). To study how physiological processes influence neuronal activity, Aβ, and AD pathogenesis, David Holtzman is exploring the sleep-wake cycle in animal models of AD and in people. Often, even before memory loss begins, AD patients experience a disruption of the normal sleep-wake cycle, with increased wakefulness. Holtzman's

studies suggest that the sleep-wake cycle does regulate the Aβ protein and promotes the accumulation of amyloid in the brain. Further, disruption of the sleep-wake cycle may be an early functional indicator of brain dysfunction due to Aβ accumulation even prior to cognitive decline.

Cortical Physiology in Humans: From Bench to Bedside

Bob Knight, MD (University of California, Berkeley)

The prefrontal cortex (PFC) is where we decide what to do or say, and Robert Knight believes that signals from the PFC and speech areas in the temporal lobe could eventually control devices to help patients who, for example, cannot speak. Using a fine EEG grid implanted on the brain of volunteers who require brain surgery, he analyzes the spatial and temporal patterns of the neural activity and cross talk among brain regions during cognitive tasks. Knight's lab is applying these findings to understand how the PFC implements human cognition. They are also comparing signals from the EEG grid when a volunteer speaks and imagines speaking the same word, and then playing it back as an auditory signal. They hope to capture and translate into auditory signals the words patients with disabling neurological disorders such as aphasia or ALS are thinking but cannot say.

Order from Disorder: Internal Representations of the Olfactory World

Richard Axel, MD (Columbia University)

Richard Axel described the representation of olfactory information in higher brain centers. This representation, or map, must translate sensory information into appropriate behavioral output. Axel argued that sensory systems do not passively represent the external world. Rather, they must actively interpret features of the world that are combined in higher brain centers to construct meaningful sensory representations. Axel demonstrated that olfactory perception is initiated by the recognition of odorants by randomly distributed sensory neurons in the nose. In the nose, olfactory sensory neurons are programmed to recognize specific odorants, but these nerve cells are randomly distributed in the nasal epithelium. Order emerges from this disorder when axons from neurons expressing the same olfactory receptor type converge on the same point, a glomerulus, in the olfactory bulb. The quality of an odor is represented by different spatial patterns of activated glomeruli in the bulb.

How does the animal look down on this pattern and discern the nature of the odor and elicit an appropriate response? Axel has traced the connections from individual glomeruli to higher olfactory centers. He then used optogenetics to silence the projections to observe which centers are responsible for innate and learned behavioral responses to odors. Projections to the cortical amygdala reveal stereotyped patterns of connectivity, suggesting that this structure may mediate innate olfactory-driven behaviors, like a mouse trembling at fox urine. Indeed, in mice in which this brain region is silenced, they no longer avoid fox urine.

In the piriform cortex, the glomeruli projections disperse with no spatial order. Unlike the other senses, cells in the piriform cortex are preferentially tuned to a specific odor, but the ensemble of neurons responding to an odor is broadly dispersed rather than clustered. Axel suggested that this disorder implies that the meaning of the odor must be imparted by learning and experience. While a given odor elicits a distinct, persistent pattern in one individual, the pattern will vary among different individuals. Thus, patterns of neural activity can have no inherent meaning. Rather, meaning is imposed by experience. Thus, the piriform cortex mediates learned olfactory behaviors.

Transcriptional and Epigenetic Mechanisms of Drug Addiction

Eric J. Nestler, MD, PhD (Mount Sinai School of Medicine)

What are the detailed mechanisms by which drugs of abuse induce long-lasting changes in gene expression in the brain, leading to addictive behavior? As a case in point, Eric Nestler looked at one transcription factor, ΔFosB, which is induced by virtually all drugs of abuse in brain reward regions. By searching the genome-wide changes in histone and chromatin modifications in these regions that accompany ΔFosB induction following chronic drug administration, he

identified numerous signatures for altered levels of gene expression in addiction. This improved understanding of how drugs alter the structure and function of brain reward neurons that underlie addiction-related behaviors may inform efforts to improve diagnostic tests and treatments for addictive disorders.

What controls sleep? Using a fly to determine the molecular underpinnings

Amita Sehgal, PhD (University of Pennsylvania, The Mahoney Institute)

Sleep is controlled by both the circadian clock that sets the 24-hour cycle and homeostasis that drives the need to sleep and regulates the amount of sleep. Amita Sehgal studies the control of both processes in the fruit fly. The fly generates the circadian clock through the cyclic expression of proteins that build up and are then degraded, so that their level tells the animal the time of day. Similar mechanisms were subsequently found to comprise the clock in humans. Many neurotransmitters are known to affect sleep and wakefulness in both human and fly homeostatic systems, but these provide an incomplete understanding. Sehgal uses unbiased genetic screens to discover new genes and molecules involved in sleep. She identified a mutant fly that sleeps 80% less than normal, and is investigating its mutant gene, which affects the level and activity of a specific potassium channel. These studies appear to also be relevant to sleep disorders in humans.

Nothing Endures but Change: Rapid Translational Regulation of Neurogranin in Response to Experience and Activity

Weifeng Xu, PhD (Picower Institute at MIT)

Our experiences in the world constantly influence the connectivity within our brain, which changes how we detect and remember the world. Weifeng Xu discovered that exposing mice to fear or new context rapidly increases the level of neurogranin, a protein that regulates calcium signaling in neurons and that is important in learning and memory. Her in vitro studies then showed that over-expressing neurogranin increases neuronal excitability, while down regulating it decreases neural firing. That can shift the threshold for brain plasticity, and influence experience-dependent changes in the brain underlying learning and memory. Xu believes that dysregulation of neuron excitability and output may underlie the cognitive impairments manifested in neurological and psychiatric disorders.

Rethinking Emotion

Joseph LeDoux, PhD (New York University)

Since Darwin, people commonly assume that basic emotions like feelings of fear or pleasure are innately wired in the brain because they help organisms adapt and survive. But do the brain circuits giving rise to these emotions/feelings also control innate responses that accompany these feelings (freezing or fleeing in fear)? LeDoux believes not. The innate circuits that detect and respond to stimuli are survival circuits. Feelings result from the awareness of the activity of these survival circuits and their consequences, including various blends of information about the stimulus and context that the survival circuit is responding to, changes in brain arousal, feedback from bodily responses, and cognitive processes that assess significance. “Understanding survival functions does not require that we understand consciousness, but understandings feelings does.”

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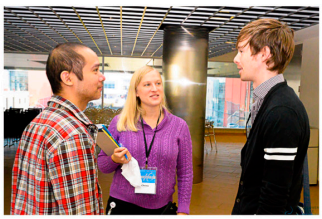

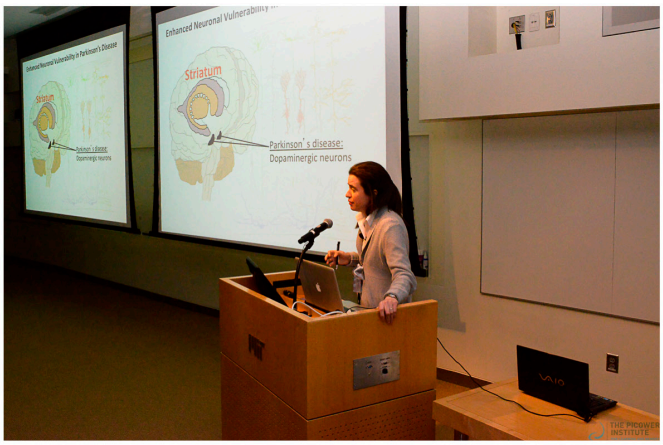

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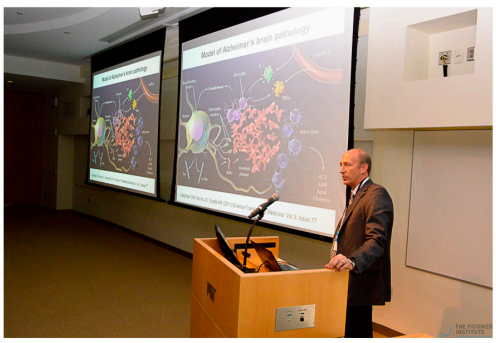



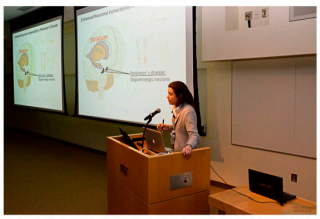







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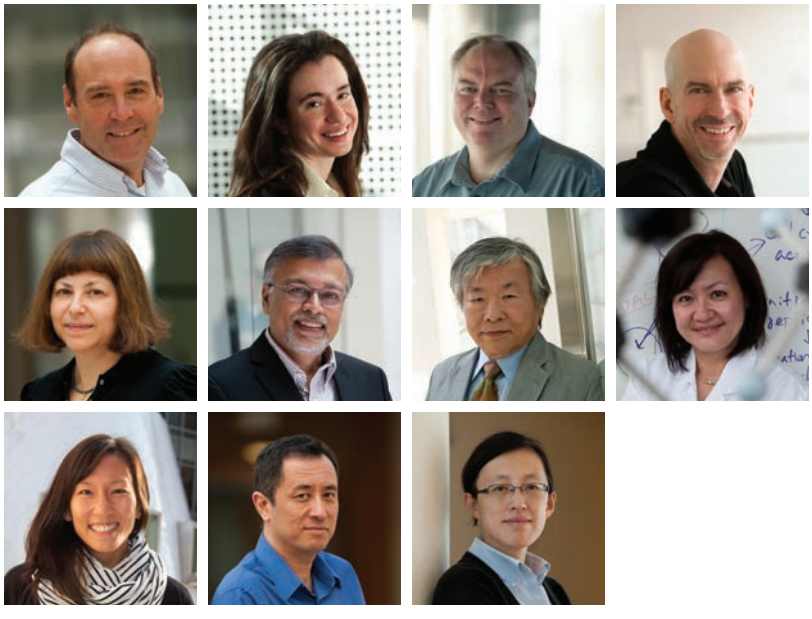

TOP ROW: Mark F. Bear, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Investigator, Howard Hughes Medical Institute (HHMI); Myriam Heiman, Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences, Broad Institute core member; Troy Littleton, Picower Professor of Biology and Neuroscience, Departments of Biology and Brain and Cognitive Sciences; Earl Miller, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences.
MIDDLE ROW: Elly Nedivi, Professor, Departments of Brain and Cognitive Sciences and Biology; Mriganka Sur, Paul E. Newton Professor of Neuroscience; Director of The Simons Center for the Social Brain; Susumu Tonegawa, Picower Professor of Biology and Neuroscience, Departments of Brain and Cognitive Sciences and Biology, Alumni Investigator, Howard Hughes Medical Institute, Alumni Investigator and Director of the RIKEN-MIT Center for Neural Circuit Genetics; Li-Huei Tsai, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Director, The Picower Institute for Learning and Memory, Investigator, Howard Hughes Medical Institute.
BOTTOM ROW: Kay Tye, Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences, Matthew Wilson, Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology, Associate Director, The Picower Institute for Learning and Memory; Weifeng Xu, Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences.

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