Neuroscience News

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THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY

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Photo/Azeddine Tahiri

FROM THE DIRECTOR

LI-HUEI TSAI

I think I can speak for all of us at the Picower Institute when I say that we have been energized by the 5th annual Dana and Betty Fisher Retreat that took place on June 25 and 26, 2012. The idea of this retreat was born under the leadership of my predecessor, Mark Bear, who was working with the Dana and Betty Fisher Foundation. The foundation was looking for novel ways to support efforts that further the knowledge of learning and memory. Together, the institute and foundation envisioned a retreat where we could all learn from each other and interact in ways not possible on a day-to-day basis in our individual laboratories.

Since our first retreat in 2007, we have seen the vision materialize. For the retreat, each laboratory led by a Picower Institute principle investigator selects a graduate student or postdoctoral researcher to present a research project to the community. Besides providing valuable practice for scientific meetings, these presentations introduce young researchers to those in other labs, and also stimulate ideas for cooperative projects. I am grateful to the Fisher family for endowing the retreat and providing an opportunity for us to form new collaborations, because that is how we will find solutions to problems that are too complex for one-dimensional approaches.

For the 5th annual Dana and Betty Fisher Retreat, we returned to the Red Jacket Inn in Yarmouth on Cape Cod, where we had such a productive and fun time last year.

We started with a full afternoon of presentations by lab members, and a keynote address entitled "The Hippocampus in Space and Time" by Dr. Howard Eichenbaum, a prominent neuroscientist and University Professor at Boston University. After browsing the poster session to learn about other work at the institute and at institutions where some of our researchers collaborate, we enjoyed a clambake dinner by the sea and kicked up our heels on the dance floor. The next morning brought more presentations, which you can read about on the next two pages.

I am so proud of the high quality of the presentations and the speakers, and of the entire vibrant research community at the Picower Institute. We returned to our labs refreshed and inspired for new discoveries, and we will be reporting many of those discoveries at next year's retreat!

COVER:
Photo courtesy of the Red Jacket Resort

DAY 1 PRESENTATIONS

The effect of chronic stress on learning and memory
Damien Rei (Tsai lab)

Chronic stress, a risk factor for the learning and memory deficits in Alzheimer's disease (AD), is mediated by the amygdala, the brain's stress center. Postdoctoral associate Damien Rei combined optogenetics and inhibitory Gi-DREADD in mice to selectively activate and deactivate neurons in specific brain regions. He found that activating the basal lateral amygdala (BLA) mimics the detrimental effect of chronic stress on learning and memory, whereas inactivating it protects against these deficits. To translate the findings to the study of AD, Rei plans to see if activating or inactivating BLA accelerates or slows down the progression of the disease in mouse models of AD.

Fear memory recall
Steve Ramirez and Xu Liu (Tonegawa Lab)

To explore the cellular basis of fear memories, graduate student Steve Ramirez and postdoctoral associate Xu Liu combined optogenetics with a system for labeling the neurons that become active in the dentate gyrus (DG) of the hippocampus as mice learn to fear a particular scary context. Later, the researchers could activate just those neurons by pulsing light through tiny optic fibers implanted in the DG. This activation re-triggered the mice's fear even while they were in a safe context. The ability to precisely control defined neurons that were activated during an event allows researchers to probe the underlying nature, and the spatial/temporal dynamics, of episodic memories.

Learning when to see what
Jeff Gavornik (Bear Lab)

Researchers have long assumed that V1, the first region of the primary cortex to process visual information, only recognizes the "where" of an image's lines, edges and curves. But postdoctoral fellow Jeff Gavornik found that V1 also recognizes the "when" of images as they appear in temporal relation to other images. He trains mice on visual recognition tasks and shows them predictable sequences of visual stimuli while recording from V1 neurons. By then varying the sequences from what the mice learned to expect, he found that the brain predicts what will come next, suggesting that higher-order processing is already occurring very early in visual recognition.

Glial calcium signaling and neuronal hyperexcitability
Jan Melom (Littleton Lab)

Cortical glial cells, once considered mere helper cells, can actively contribute to brain function – and dysfunction, including seizures and epilepsy. Graduate student Jan Melom studies zydeco, a mutant Drosophila (fly) that "dances" when seizing upon changes in temperature or mechanical stimulation. She found that the zydeco gene affects a calcium exchanger at the membrane and eliminates normal calcium oscillations at the glial membrane, and that calmodulin is required for the seizures. She hypothesizes that acute disruption of calcium signaling in glia can impair neuronal function and lead to seizure, and she is identifying suppressors of zydeco that may translate to treating human disorders.

Keynote Address by Howard Eichenbaum: *The hippocampus in space and time*

Neuroscientist Dr. Howard Eichenbaum, a University Professor at Boston University, promised to reconcile the disconnect between two views of the hippocampus, which in humans supports episodic memories that unfold in time and in rats creates cognitive maps of the environment to support navigation through space. Previous research has documented that when rats learn to run a maze, "place cells" fire in specific patterns to represent the event. By designing experiments for rats to learn the sequence of odors, Eichenbaum recently showed that "time cells" also fire, creating a temporal representation of the event. (There may also be "distance cells" tracking how far a rat has moved!) He is now investigating where in the brain this temporal signal arises, possibly from the medial entorhinal area, which is a hub in the memory and navigation network. His work contributes to an emerging view that the hippocampus creates a scaffold for the context in which an event occurs and parses its dimensions into smaller units of what, where and when.

DAY 2 PRESENTATIONS

Translational regulation of neurogranin levels
Kendrick Jones (Xu Lab)

How do levels of neurogranin, a protein that regulates calcium signaling in neurons, vary in response to experience? Postdoctoral associate Kendrick Jones showed that in mice, the experience of acute fear enhances neurogranin levels in the hippocampus. In cultured cortical neurons that were activated to recapitulate that experience-dependent increase, adding norepinephrine enhanced the size and speed of this neurogranin increase via the new translation of pre-existing mRNA. Also, increasing neurogranin levels in hippocampal slices led to an increase in neuronal excitability, while decreasing neurogranin reduced excitability. Jones is now investigating the impact of manipulating neurogranin levels on behavior in mice.

Thalamus and hippocampus during slow wave sleep
Hector Penagos (Wilson Lab)

Matt Wilson's lab previously showed that during slow wave sleep, hippocampal place cells replay the firing patterns that developed as a rat ran a maze. Postdoctoral associate Hector Penagos looks at the less-studied role of the anterior thalamus in episodic memory and spatial navigation. He recorded from both "head direction cells" in the thalamus and hippocampal place cells as rats navigated a maze and later dreamed about. When place cells burst during sleep, head direction cells were silent, and visa versa, as if they were taking turns talking and listening. Penagos is now investigating how thalamus cells bias what the hippocampus encodes and influence the content of the hippocampal replay.

Visualization of synaptic dynamics in vivo
Katie Villa (Nedivi Lab)

The connections between neurons change over time, enabling new learning and memory to occur. Previously, the Nedivi Lab found that excitatory dendritic arbors remain stable while inhibitory dendrites and axons are plastic, constantly remodeling their connections with excitatory cells. Graduate student Katie Villa, working with former graduate student Jerry Chen and current graduate student Kalen Berry, developed a technique for visualizing inhibitory synapses on excitatory cells over time. These images revealed the dynamic rearrangement of inhibitory synapses on the dendritic shafts and spines, and showed that changes in inhibitory synapses are coordinated with changes in excitatory spines.

Novel pathways for optogenetic control of anxiety
Ada Felix-Ortiz (Tye Lab)

Kay Tye's lab has been up and running for just five months, and for its first presentation at a Picower retreat, research associate Ada Felix-Ortiz presented new preliminary data from optogenetic experiments looking at parallel circuits involved in anxiety. She uses optogenetic projection-specific targeting techniques to investigate the inputs from the basolateral amygdala to cortical and hippocampal regions. Felix-Ortiz will next combine optogenetics with electrophysiology to provide a systems-level mechanistic explanation of this behavioral phenomenon.

Synchronous neural ensembles for rules
Eric Denovellis (Miller Lab)

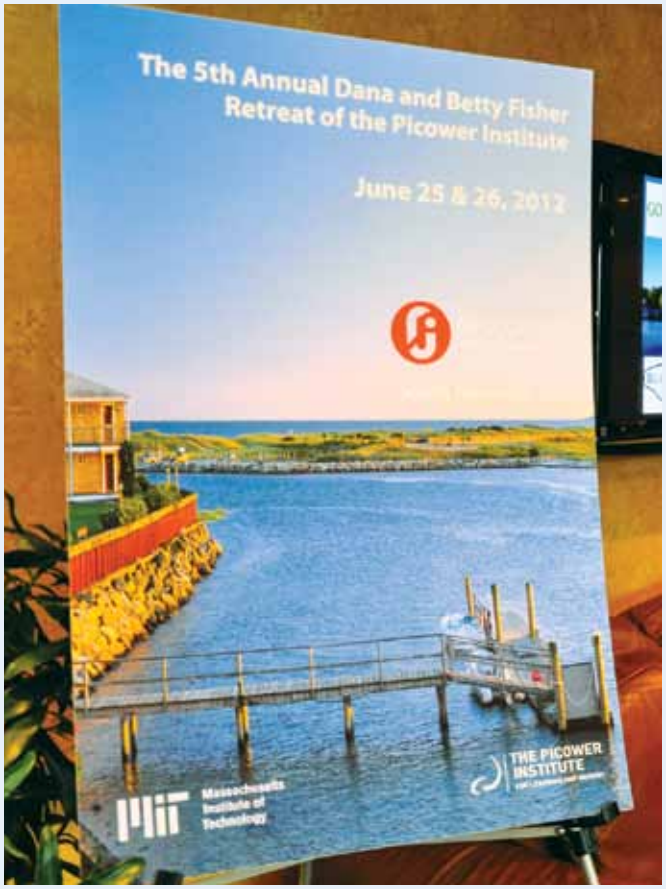
What are the neural mechanisms that support our flexibility in applying rules of behavior to different situations? With collaborators in the Miller Lab, research affiliate Eric Denovellis recorded from neurons in the prefrontal cortex (PFC) while monkeys switched between two rules: attending to an image's color versus its orientation (the more dominant rule). Analyzing the oscillatory synchronization that encoded each rule showed that beta-frequency synchrony selects the relevant rule ensemble, while alpha-frequency de-selects a stronger, but currently irrelevant, rule. Denovellis proposes that synchronous activity in PFC is a mechanism that allows us to follow specific rules but to change dynamically as demands change.

Differential vulnerability in Huntington's Disease
Robert Fenster (Heiman Lab)

Robert Fenster is a visiting scholar in the Myriam Heiman Lab, which investigates the selective vulnerability of medium spiny neurons of the striatum and deep cerebral cortical neurons in Huntington's Disease (HD). The basis for this enhanced vulnerability is unknown, but could potentially be targeted therapeutically. By analyzing cell-type specific information in a mouse model of HD, they demonstrated that the most vulnerable neurons express high levels of polyglutamine-containing proteins. They hypothesize that over-expression of polyglutamine proteins leads to the characteristic huntingtin aggregation and cell death in HD, and they have validated a primary culture model system to directly test this hypothesis.

Distinct cortical inhibitory networks in vivo
Caroline Runyan (Sur Lab)

Postdoctoral fellow Caroline Runyan has expanded upon work from Mriganka Sur's lab that Nathan Wilson first reported at last year's retreat. They use optogenetics to activate specific types of inhibitory cells, either as a population or one cell at a time, while using new functional imaging methods to measure the effects on visual responses in neighboring cells in the primary visual cortex. They are asking: what are the functional impacts of the activity of specific inhibitory cell types, and to which neurons in the local network do single inhibitory neurons functionally connect? Their findings suggest that inhibitory neuronal subclasses have distinct and complementary roles in cortical circuits.



Researchers enjoyed a clambake dinner by the sea and kicked up their heels on the dance floor.

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Researchers Attending The 5th Annual Dana & Betty Retreat of the Picower Institute

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