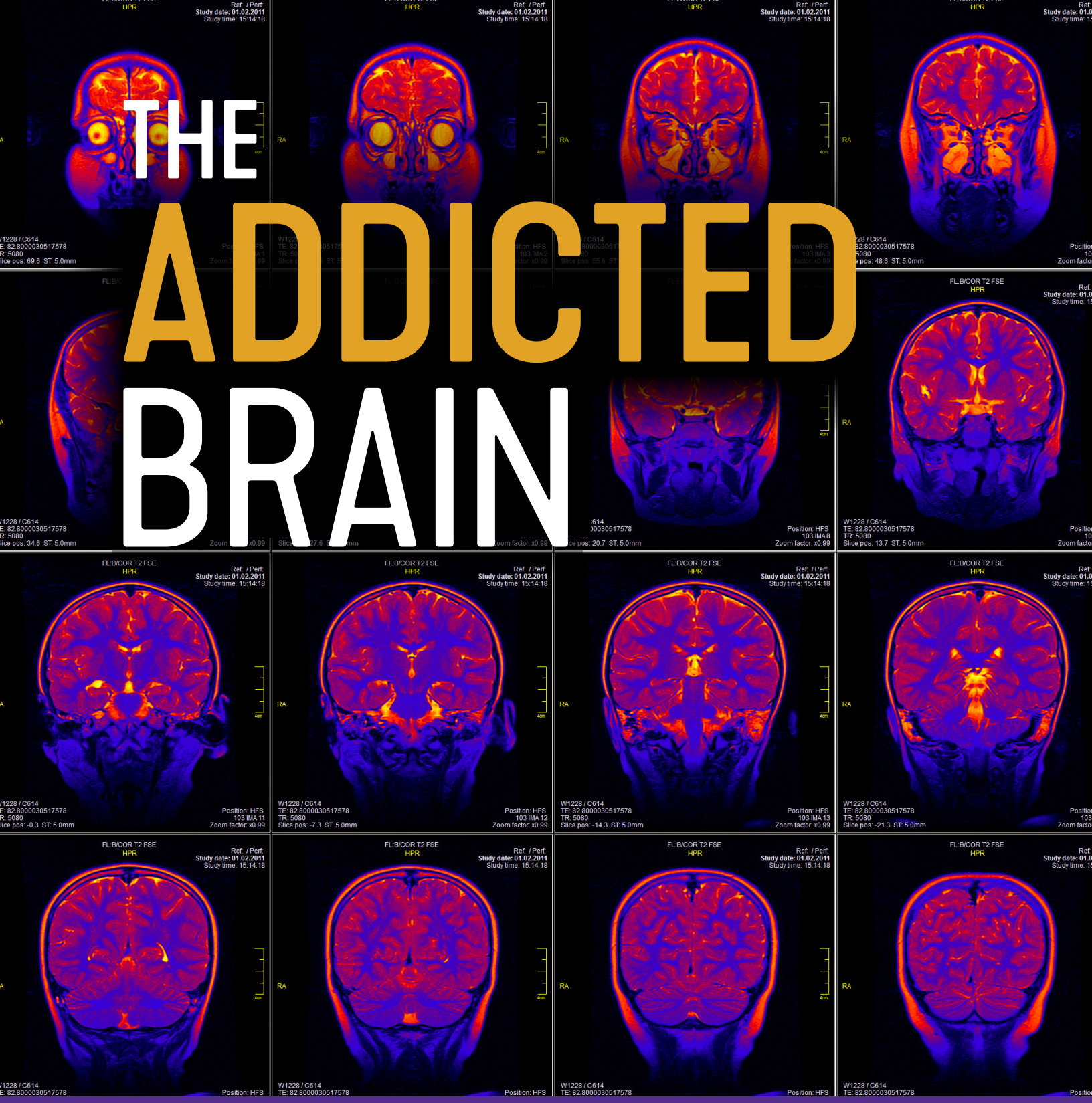


THE ADDICTED BRAIN

Neuroscience News

MIT FALL 2017

THE PICOWER INSTITUTE FOR LEARNING AND MEMORY

DIRECTOR'S **MESSAGE**

Dear Friend,

One doesn't need to look far to witness firsthand the ravages of addication in our society today. While exact numbers are hard to obtain, last year, the New York Times reported that drug overdose had become the leading cause of death for Americans under the age of 50.

The more we understand how drugs affect the brain and the neural processes that lead to dangerous chemical dependency, the more we can produce ways to counter attack this deadly epidemic. At the Picower Institute, we have several investigators who are exploring these pathways, and their work shows great promise in moving us closer to the day when we can make a positive impact on curbing and treating addiction. This month's feature article explains how.

If you have been following the Picower Institute for any length of time, you know what distinguished scientists and staff we are so fortunate to have here. In this month's issue, we highlight one of our rising stars, Kay Tye, whose work to understand how the brain processes external information to recognize risk or reward is lending great insights into understanding mental health. Her personal story of how she came to choose a career in research spurns out of her own parents' drive to seek reward, despite great risks.

Finally, I am always happy to present our section on recent publications of discoveries made here at the Picower Institute. In this issue, I am honored to have my work featured alongside that of Susumu Tonegawa and Kay Tye as we explore how memories are retrieved, how and what neurons allow us to make quick decisions, and how turning off an enzyme that, when over-expressed, shuts down neural plasticity may be a way to treat Alzheimer's disease.

Thank you again for your interest in the Picower Institute. Please enjoy this issue of Neuroscience News.

LI-HUEI TSAI
Director, Picower Institute

Addiction: Deficits in the Mechanisms of Learning and Memory

In this **ISSUE**

The economic and social impact of drug use regularly makes headlines around the world. In contrast, the long-term impact of compulsive drug use on brain function receives little media attention.

To better understand the experiences of drug users, and create practical treatments for addiction, it is important to understand the fundamental changes that occur in the affected brain.

Research into the mechanisms of learning and memory at the Picower Institute is shedding light on the fundamental brain functions disrupted by addiction, and may help to create potential therapies that ameliorate disrupted brain activity.

Front cover: A series of MRI brain scans.

Drugs Hijack Dopamine Release and Synaptic Plasticity

Addiction causes harm to the brain, in part, by damaging the mechanisms of learning and memory. Learning and memory formation causes changes in the communication between neurons through a process known as synaptic plasticity, or a change in the strength of neuronal connections.

Addictive drugs hijack synaptic plasticity through the neurotransmitter dopamine. The ventral tegmental area (VTA) -- a primary source of dopamine -- typically releases the neurotransmitter when something rewarding happens, or when a novel experience occurs. This in turn enhances attention and memory formation, which are functions of the prefrontal cortex and hippocampus, respectively. Habitual drug use causes the VTA to become dysfunctional, leading to excessive dopamine release. It also dysregulates connectivity and communication between brain regions, which negatively alters motivation, associative learning, and other cognitive functions.

Dopamine's effects are so strong and wide that it can permanently change the brain, making addiction incredibly difficult to overcome. To treat addiction it is necessary to restore the normal mechanisms of learning and memory and dopamine release, and to identify the affected neural circuits.

Rebalancing the Circuits of the Compulsive Brain

Individuals with addiction exhibit compulsive use of drugs in the face of negative consequences, even when they do not want to use. **Assistant Professor Kay M. Tye** studies how the dopaminergic system processes motivation, reward-seeking, and compulsive behaviors.

Her team has identified a neural circuit that is made up of connections between the lateral hypothalamus and the VTA. Findings from her lab have shown that inhibiting these connections results in decreased compulsive behavior.

In this way it is hoped that developing treatments that inhibit the connections between the lateral hypothalamus and the VTA and downstream projections to the ventral striatum (a center linked to the experience of reward/pleasure) in those with addiction could help short circuit compulsive drug use.

Stopping drug use is only one half of the problem of managing addiction, however. It is equally important to maintain sobriety. Environmental cues can make this process more difficult, by creating strong drug cravings.

So for example, someone addicted to alcohol will associate a specific bar with the rewarding feelings of drinking. Dopamine modulates both the feelings of reward and the association between drinking and the context. To help maintain sobriety, it is important to understand how dopamine regulates this associative learning process.

Picower Professor Susumu Tonegawa has studied the genetic basis of associative learning, memory, and synaptic plasticity for over 20 years. His lab has shown that dopamine is critical for synaptic plasticity and boosting neuronal activity of the hippocampus, a brain region critical for associative learning.

Researchers from his lab found that dopamine is released into the hippocampus when exploring a new environment. When hippocampal dopamine receptors are removed in mice, the animals cannot tell the difference between a familiar and novel environment.

Moreover, these mice show deficits in associating an environment with experiences in that environment, suggesting that targeting hippocampal dopamine receptors could provide ways to treat cue-induced drug cravings.

Dopamine is also important for synchronizing multiple brain regions to coordinate cognitive function and behavior. Coordinated activity between the VTA, hippocampus, and the prefrontal cortex help drive goal directed behaviors like trying to find a reward at the end of a maze.

Those with addiction are overly driven to find reward, such as drugs. Such compulsivity has been shown to be due, in part, to heightened brain synchrony.

To treat addiction it is necessary to restore the normal mechanisms of learning and memory and dopamine release, and to identify the affected neural circuits.

Picower Professor Matthew Wilson studies brain synchronization between the prefrontal cortex and the hippocampus. His lab has found that when a rodent is exploring a maze in search of a reward, the hippocampus and prefrontal cortex synchronize when the animal chooses the correct path.

However, when the animal chooses the incorrect path there is a reduction in synchrony between the prefrontal cortex and hippocampus. Finding ways to diminish brain synchrony may help reduce drug seeking, and perhaps buffer against cues that increase craving.

Drug addiction disrupts the mechanisms of learning and memory by altering VTA activity, chronic dopamine release, and synaptic plasticity.

Research at the Picower Institute has shown that inhibiting the VTA-lateral hypothalamus circuit reduces compulsive behavior, while targeting hippocampal dopamine receptors may prevent cue-induced drug cravings, and understanding how brain synchrony drives goal directed behaviors can stave off drug seeking.

In studying the mechanisms of learning and memory, Picower faculty have provided potential targets that may help create therapies to treat millions of people with addiction.

JOSHUA SARIÑANA, PhD

Mapping Memory Retrieval

Picower Professor Susumu Tonegawa

Making memories requires activation of neurons and changes in the way those neurons communicate.

Researchers have previously believed that retrieving memories requires reactivation of the same neurons that were active during their formation. However, very little was known about how the process of memory retrieval actually works.

To see if memory formation and retrieval rely on the same neuronal circuits, researchers in the lab of **Picower Professor Susumu Tonegawa** looked at two regions critical for learning and memory, the hippocampus and entorhinal cortex. In particular, the researchers studied how information is transferred from the hippocampus to the entorhinal cortex during memory formation and retrieval.

Tonegawa's team discovered that a hippocampal subregion called the subiculum is crucial for memory retrieval, which they called the indirect circuit. The researchers then found that information for memory formation bypasses the subiculum and is sent directly the entorhinal cortex, which they called the direct circuit.

By turning off the indirect circuit using optogenetics – a tool that can turn off or on neuronal circuits with light – the researchers were able to impair memory retrieval, but not formation. In contrast, when they turned off the direct circuit memory formation was impaired, but not memory retrieval.

For the first time, the researchers have identified a causal role for the subiculum in memory recall. The team has also established that two distinct circuits are activated for memory formation and retrieval.

■ Published in **Cell**

Distinct neural circuits for the formation and retrieval of episodic memories. Roy, Kitamura, et al. Cell

Picturing Neuronal Activity at Any Given Moment

Assistant Professor Kay M. Tye

Many cognitive processes, such as decision-making, take just seconds or minutes to complete. Neuroscientists have long wished to capture neuronal activity during such tasks, but that dream has remained elusive.

Now a team of researchers formed between the labs of Kay M. Tye at MIT and Alice Y. Ting and Stanford University has developed a way to label neurons when they become active, essentially providing a snapshot of their activity at a given moment in time. This approach could offer significant new insights into neuron function, by offering greater temporal precision than current cell-labeling techniques, which capture activity across time windows of hours or days.

"A thought or a cognitive function usually lasts from 30 seconds to a minute," says **Assistant Professor Kay M. Tye**. "That's the range of what we're hoping to be able to capture."

The technique, called FLARE, will allow neuroscientists to label and then manipulate sets of neurons that are active during specific tasks.

FLARE opens up a wide range of studies that have been previously impossible, says Tye. For example, the tool could be used to help decipher the neural circuits involved in learning and memory, investigate what happens as the brain makes quick decisions, and identify the function, location, activity and connectivity of any group of neurons active at a given time.

■ Published in **Nature Biotechnology**

A light- and calcium-gated transcription factor for imaging and manipulating activated neurons. Wang, Wildes, et al. Nature Biotechnology June 26, 2017

De-Repressing Gene Expression to treat Alzheimer's Disease

Picower Director Li-Huei Tsai

Managing which genes turn off or on is critical for proper brain function. One way by which genes turn off is through an enzyme called HDAC2.

HDAC2 is known to repress the gene activity responsible for synaptic plasticity, or how communication between neurons changes in response to experience.

When the amount of HDAC2 present in mice is artificially increased, it leads to cognitive impairments. It has also been shown that both mice with Alzheimer's disease, and human Alzheimer's patients, exhibit elevated levels of HDAC2.

As a result, researchers believe that using therapeutics to reduce elevated levels of HDAC2 may help treat Alzheimer's disease and other neurological disorders. Unfortunately, however, HDAC2 inhibitors are not very specific, and can produce unwanted side effects.

Researchers in the laboratory of **Picower Director Li-Huei Tsai** have developed a way to specifically disrupt HDAC2 interaction with synaptic plasticity genes. By utilizing weighted correlation network analysis -- a data mining tool that identifies genes that interact with others -- her team has discovered a protein that cooperates with HDAC2 called Sp3. Like HDAC2, Sp3 levels are also elevated in mice with Alzheimer's disease and Alzheimer's patients.

When the researchers reduced Sp3 levels, the amount of HDAC2 found at genetic locations that regulate synaptic plasticity was also reduced. Targeting Sp3 offers a novel and more accurate way to decrease HDAC2 activity, and a potential target in finding therapeutics to treat Alzheimer's disease.

■ Published in **Cell Reports**

Yamakawa, Cheng, et al. Cell Reports

Cookies, Conversation, and Collaboration:

THE ANNUAL PICOWER SUMMER RETREAT PROVOKES, MOTIVATES, AND INSPIRES

Members of the Picower Institute play a friendly game of volleyball in between science presentations.

New England weather is fickle, so few were surprised that an early June weekend on Cape Cod was cold and rainy. But the clouds and drizzle had no chance of dampening the spirits of the Picower Institute community who descended upon the Red Jacket Beach Resort in South Yarmouth for the 10th annual retreat.

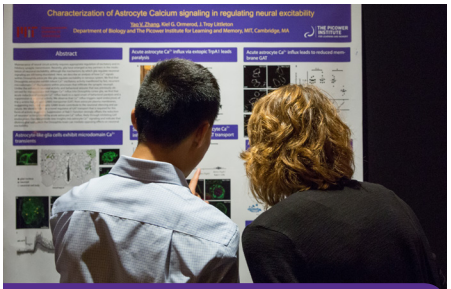
This annual event is made possible by the generosity of Wendy Fisher, who in 2008, along with her siblings, established an endowment at the Picower to enable the community to come together in a casual and relaxed setting. Named in honor of their parents, the Dana and Betty Fisher Retreat is marked by laughter and lively conversations as much as it is by posters and presentations. A highlight of the evening activities was the spirited karaoke competition that Picower Institute Director Li-Huei Tsai said she was particularly excited for.

Amongst the fun and abundant trays of cookies, brownies, and fruit kebabs, however, was the serious sharing of research, giving the rising stars of the Picower Institute, the graduate students and post docs, an opportunity to make presentations and prepare posters to show their work to their colleagues. Over the two days, attendees were treated to presentations of research from 10 faculty labs and 22 poster presentations; seven posters featured work from the lab of Troy Littleton.

Graduate student Caitlin Vander Weele from Kay Tye's lab won best poster, with her submission entitled "Dopaminergic Modulation of Prefrontal Cortex Subpopulations." The team of graduate student Amanda Vernon and post doc Dipanwita Ghose from Myriam Heiman's and Weifeng Xu's labs won the prize for best talk with their presentation entitled "Enhanced Stratal Glutamatergic Function Upon Chronic Antipsychotic Administration. "

Studying the brain is an intense endeavor. The annual retreat, thanks to the good foresight and support of Wendy Fisher and her family, provides a welcome respite while also offering the opportunity to spark new conversations and collaborations with colleagues. The reinforced camaraderie that emerges will have a lasting effect on the Picower and all it can accomplish.

Picower Director Li-Huei Tsai gives opening remarks.



Researcher's discuss their newest findings.

Faculty Profile:

Kay M. Tye

When Mao Zedong's Communist Party took over China in 1949, Kay Tye's grandmother was forced to flee Shanghai for Hong Kong, leaving all her possessions behind.

Seeking a better life, Tye's father later took a ship from Hong Kong to the U.S., meeting his future wife on board.

A theoretical physicist and a biochemist, the pair went on to build successful careers at Cornell University, but their background would go on to have a big impact on Tye.

"The one thing I took away from my parents' background is that knowledge is the purest commodity, and your education and experiences are the one thing that no-one can ever take away from you," says Tye, an assistant professor in the Department of Brain and Cognitive Sciences at MIT and a member of the Picower Institute for Learning and Memory.

Despite this, Tye was not initially drawn to research, and flirted with the idea of a number of different career paths after graduating from MIT with a degree in Brain and Cognitive Sciences in 2003.

"But then I realized that there is something amazing about a career in research, in terms of the creative freedom, and the ability to wake up in the middle of the night with an idea, scribble it down, and then spend the next few years making that vision a reality," she says. "That is something I really cherish."

Tye's research lies in investigating how the brain processes emotional and social information, and identifying the specific circuits involved in this activity. She uses optogenetic, electrophysiological, pharmacological and imaging techniques to better understand the way in which the brain reacts to internal and environmental stimuli, allowing us to make snap decisions on how to act.

This ability to instantly evaluate even competing information from the environment and immediately respond is essential for survival, and is a key feature of mental health.

In particular, Tye is interested in discovering why the processing of both positive and negative emotions is located in the same area of the brain, and why the neurons that perform these functions are so closely intermingled.

Tye is also investigating how the brain associates certain stimuli with punishment or reward, and how this can be altered depending on the external situation or the internal state. So, for example, receiving the same card in a game of poker can be either good or bad, depending on what cards the player is already holding and on intuitions about what cards other players may have.

Similarly, Tye is also interested in how hunger can have such a strong influence over our emotional processing and cognitive functions. She believes we have evolved in this way to help us survive. "If I am a foraging prey animal and a predator is approaching, I need to stop collecting food and run, but if I am nearing starvation, my body needs to signal to my brain that additional risks need to be taken, I can't just cower in my burrow," she says.

This evaluation of risk and reward drives many of our day-to-day decisions, from the mundane to the life-changing. Tye's own family, for example, risked everything for the potential reward of a better life in the U.S.

PICOWER Accomplishments

TROY LITTLETON

Menicon Professor in Neuroscience, Troy Littleton, received the Brain and Cognitive Sciences Award for Excellence in Postdoctoral Mentoring.

MYRIAM HEIMAN

Latham Career Development Chair Assistant Professor of Neuroscience, Myriam Heiman, recently received the Paul and Lilah Newton Brain Science Award.

Upcoming EVENTS

For a list of ongoing scientific lectures, colloquia, and workshops, please go to: **picower.mit.edu**

Fall Symposium

10.13.17

Catherine Dulac, PhD is the Higgins Professor of Molecular and Cellular Biology and chair of the Department of Molecular and Cellular Biology at Harvard University. Her lab investigates the architecture and functional logic of neuronal circuits underlying pheromone signaling and the phenomenon of genomic imprinting in the brain, and the role of this mode of epigenetic modification in brain development and adult brain function.

Barry Everitt, ScD is a Professor and Director of Research, and Provost of the Gates Cambridge Trust, at the University of Cambridge. His research is concerned with the neural and psychological mechanisms underlying learning, memory, motivation and reward especially related to drug addiction.

Steven Flavell, PhD is an Assistant Professor in the Brain and Cognitive Sciences Department and the Picower Institute for Learning and Memory at MIT. His lab's goal is to understand how neural circuits generate sustained behavioral states, and how physiological and environmental information is integrated into these circuits.

Hailan Hu, PhD is a Professor and Senior Principal Investigator at the Zhejiang University Interdisciplinary Institute of Neuroscience and Technology (ZIINT) and School of Medicine at Zhejiang University. Her lab aims to understand how emotional and social behaviors are encoded in the brain, with a main focus on the neural circuitry underlying depression and dominance hierarchy.

Zachary Knight, PhD is an Assistant Professor in the Department of Physiology at the University of California, San Francisco and a Robertson Neuroscience Investigator of the New York Stem Cell Foundation. His lab studies neural circuits in the mouse that control feeding and other motivated behaviors central to survival. Their goal is to understand how these circuits are able to sense the needs of the body and then generate specific behavioral responses that restore homeostasis.

Eve Marder, PhD is the Victor and Gwendolyn Beinfield Professor of Neuroscience in the Biology Department of Brandeis University. She studies the dynamics of small neuronal networks, and her work was instrumental in demonstrating that neuronal circuits are not "hard-wired" but can be reconfigured by neuromodulatory neurons and substances to produce a variety of outputs.

Hee-Sup Shin, MD, PhD is the Director of the Center for Cognition and Sociality Institute for Basic Science and a Principal Research Scientist at the Korea Institute of Science and Technology. His work is aimed at understanding how changes in calcium dynamics in nerve cells regulate brain functions.

Garret Stuber, PhD is an Assistant Professor in the Department of Cell Biology and Physiology at the University of North Carolina at Chapel Hill. His primary research goal is to further delineate the synaptic mechanisms and functional neural circuitry that underlie motivated behavioral processes that are perturbed in neuropsychiatric disorders such as addiction, depression, and eating disorders.

Kay Tye, PhD is an Assistant Professor in the Brain and Cognitive Sciences Department and the Picower Institute for Learning and Memory at MIT. Her lab employs an interdisciplinary approach including optogenetics, electrophysiology, pharmacology and imaging techniques to find a mechanistic explanation for how emotional and motivational states can influence learning and behavior, in both health and disease.

Aging Brain Seminar Series

11.01.17 **Richard Ransohoff, MD** is Vice President and Senior Research Fellow in Neuro-immunology at Biogen. He is a leading neuroimmunologist whose research has focused on the functions of chemokines and chemokine receptors in the development and pathology of the central nervous system.

12.06.17 **Bruce Yankner, MD, PhD** is Professor of Genetics and Neurology at Harvard Medical School, Director of the Harvard Neurodegeneration Training Program, and Co-Director of the Paul F. Glenn Center for the Biology of Aging. His work has contributed to understanding pathogenic mechanisms in Alzheimer's disease, Down's syndrome and Parkinson's disease, beginning with the initial observation that amyloid beta protein is a toxic molecule, and later with investigations into the roles of presenilin proteins, Notch and Wnt in neuronal signaling and pathology.

MIT Colloquium on Brain and Cognition

09.28.17 **Joshua P. Johanse, PhD** Team Leader of the Laboratory for Neural Circuitry of Memory at the RIKEN Brain Science Institute. His lab studies how teaching signals regulate memory formation and guide adaptive behavior.

10.05.17 **Tony Wyss-Coray, PhD** is a Professor of Neurology & Neurological Sciences at the Stanford University School of Medicine. His lab studies the role of immune and injury responses in neurodegeneration and Alzheimer's disease. They seek to understand how immune responses and injury pathways may modulate neurodegeneration and age-related changes in the brain.

11.30.17 **Cyril Herry, PhD** Researcher and Team Leader, Neuronal circuits of associative learning, at the University of Bordeaux. His lab aims at understanding the functional, anatomical and physiological properties of specific prefrontal and amygdala excitatory/inhibitory neuronal circuits involved in the acquisition and expression of Pavlovian associative learning.

Picower Lecture

10.16.17 **Fred "Rusty" Gage, PhD** is a Professor at the Salk Institute for Biological Studies, Vi and John Adler Chair for Research on Age-Related Neurodegenerative Disease. His lab concentrates on the adult central nervous system, and unexpected plasticity and adaptability to environmental stimulation that remains throughout the life of all mammals. Our lab has demonstrated that human beings are capable of growing new nerve cells throughout life in a process called Neurogenesis.

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OUR VISION

The Picower Institute is a community of scientists focused on a common question: How is the brain modified by experience?

To answer this question we use multiple levels of analysis, ranging from molecular to behavioral, and exploit the tools of modern molecular biology and genetics to dissect the contributions of specific molecules, synapses, cells and circuits to behavior.

We work to understand the pathophysiological mechanisms underlying complex disorders of the brain that affect emotion and cognition.

SUPPORT THE PICOWER INSTITUTE

For more information on our research or how to make a gift to the Picower Institute for Learning and Memory, please contact: Asha Bhakar, PhD, abhakar@mit.edu, tel: 617-258-0759.

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BOTTOM 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, Investigator, Howard Hughes Medical Institute, 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; **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.