# Neuroscience News

Summer 2014

THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY


LI-HUEI TSAI
DIRECTOR
*Picower Institute for Learning & Memory*

## FROM THE DIRECTOR

# LI-HUEI TSAI

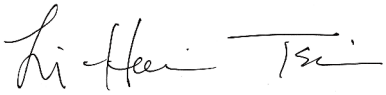
For the first time, the Picower Institute hosted its annual retreat on Cape Cod with our colleagues in the McGovern Institute for Brain Research and MIT's Department of Brain and Cognitive Sciences. Traditionally, the two institutes have separate events at the end of the academic year, but we decided to try something new in 2014. I hope all attendees enjoyed this year's early June gathering as much as I did and agree it was a great success!

The very first joint retreat brought together more than three hundred participants from the entire MIT neuroscience community. It provided an extraordinary opportunity for scientists representing different parts of this diverse community, who otherwise may seldom if ever interact, to share highlights of recent work and get to know fellow researchers working in nearby laboratories back in Cambridge. In terms of advancing our scientific research, the joint retreat helped attendees better understand how their work fits into a broader perspective. This kind of insight will likely generate promising ideas for future collaborative projects that will help us collectively find multidimensional solutions to complex scientific challenges.

Graduate students and postdocs nominated by their faculty mentors from across this unique and well-respected community delivered outstanding scholarly presentations on recent findings, both from the podium and in the poster exhibition. The two-day event's social features—a reception, clambake, and dance party—gave all of us the chance to engage in lively discussions about the talks and posters, but only the anonymous judging committee had the difficult task of choosing the best in both categories. We are especially proud of the Picower Institute's Sam Cooke (Bear Lab) and Ram Madabhushi (my lab), this year's poster presentation winners! Please find highlights of the program presentations in this newsletter.

We again thank the Dana and Betty Fisher Foundation for the generous endowment that enables the Picower Institute to host this annual retreat by the sea. This year, in particular, the event fostered invaluable conversations, connections, interactions, and learning opportunities for our staff. I am confident that together, our vibrant research community will continue to make new discoveries and groundbreaking progress in our mission to better understand the brain and advance the goals of neuroscience.

Li-Huei Tsai, Ph.D.
Director



# CONTENTS



**COVER** Researchers attending retreat
Photo credit: Azeddine Tahiri

# POSTER CONTEST
# WINNERS

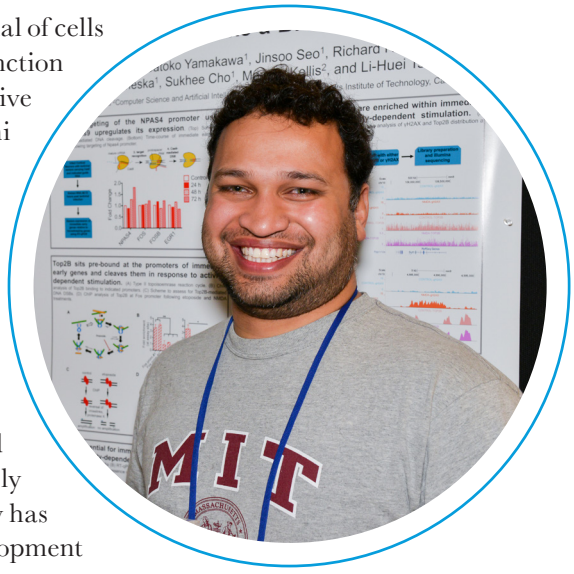
## SAM COOKE
*BEAR LAB*

### Habituation: A Model for Cortical Information Storage

An anonymous panel of judges completed the difficult task of selecting two winners from among forty-two diverse, high-quality poster presentations at this year's retreat. Winner Sam Cooke, a Picower Institute postdoctoral associate, along with collaborators from Picower, McGovern, and BCS discovered that a form of long-term recognition memory is stored via synaptic plasticity in the primary sensory cortex. Cooke and his team found that a mouse's ability to detect, remember, discriminate between, and appropriately respond to novel and familiar visual stimuli is limited to the eye that a previously viewed these stimuli. They also identified local molecular mechanisms of synaptic plasticity that support this memory within primary visual cortex. This long-term visual habituation, a fundamental and pervasive form of learning, may provide a rare opportunity to directly observe memory in the making.

## RAM MADABHUSHI
*TSAI LAB*

### Upon Activation, Neurons Take a Break

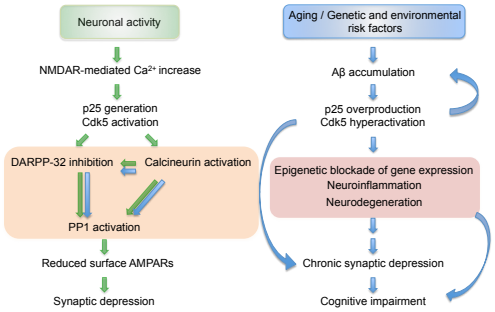



Scientists agree that damage to the genetic material of cells is likely an important cause of neuronal dysfunction as we age and in instances of neurodegenerative diseases. Postdoctoral fellow Ram Madabhushi and colleagues from Picower and MIT's Computer Science and Artificial Intelligence Lab are investigating the sources of DNA damage (double-strand breaks—DSBs) that are most relevant to neurodegeneration and whether certain neurons are more susceptible to this damage. Surprisingly, they observed that some DSBs are essential for the early expression of genes that play crucial roles in learning and memory. Their findings also suggest that timely repair of DSBs involved in critical functions likely has important implications for preventing the development of neurodegenerative diseases.

## A Common Pathway Regulating Synaptic Plasticity and Beta-Amyloid-Mediated Synaptic Toxicity

JINSOO SEO, TSAI LAB, (PICOWER INSTITUTE)

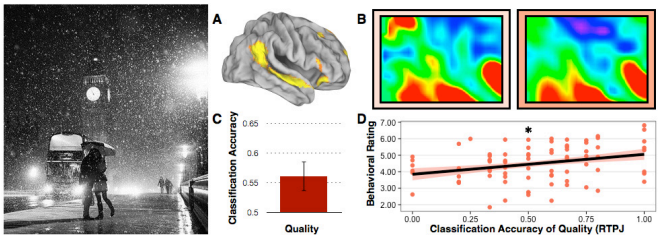
While scientists have known about the CDK5 molecule and its protein activator p25 for decades, postdoctoral fellow Jinsoo Seo and others recently discovered that this pathway impacts multiple neuronal functions, and plays both a positive and negative role in synaptic plasticity. Under physiological conditions, p25 regulates synaptic function that is critical for synaptic depression and memory extinction. However, under pathological conditions such as Alzheimer's disease, chronic expression of p25 induces neurodegeneration and synaptic weakening that can lead to cognitive impairment. Seo and others plan to use these findings to develop new therapeutic strategies for Alzheimer's and related diseases.




## Mentalizing Regions Explicitly Code Quality and Source Information about Others' Beliefs

JORIE KOSTER-HALE, SAXE LAB (MCGOVERN INSTITUTE)

Can you guess what the person sitting next to you is thinking about and what she might do next? Cognitive neuroscience graduate student Jorie Koster-Hale's work focuses on theory of mind: the capacity to predict and explain other people's actions based on their thoughts and feelings at the time. Making inferences about what's happening in the minds of others and how they might act underlies many of our social interactions. So how do we determine what somebody believes and how he might behave; in other words, how do we know what other people know? Koster-Hale points to two key computational components—source of belief (seeing versus hearing, for example) and quality of evidence—tracked and coded in a specific region of the brain associated with social cognition. These representations are based on generalized input versus direct first-person experiences. This research represents a first and significant step in discovering the neural processes that enable us to reliably predict others' behavior.

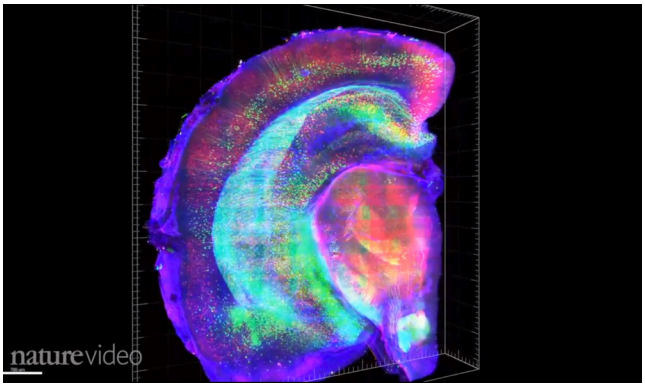



*In (A) the RTPJ, a brain region implicated in social reasoning, the (B) pattern of neural activity (C) tracks information about why other people believe what they believe (in particular, the quality of their evidence), and (D) reliably reflects behavioral sensitivity to gradient differences in evidence quality.*

## Rapid and Quantitative 3D Molecular Phenotyping of Intact Brain

SUNG-YON KIM, CHUNG LAB, (PICOWER INSTITUTE)

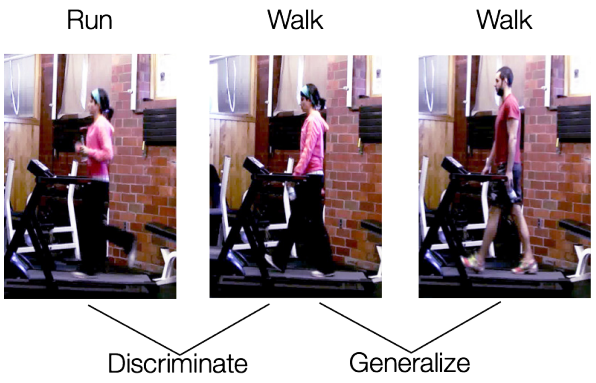
Picower's Chung Lab, less than a year old, welcomed postdoctoral fellow Sung-Yon Kim last September. He began his retreat presentation by talking about CLARITY—invented by his faculty advisor Kwanghun Chung—a technique that renders optically transparent, permeable brain tissue while preserving molecular and structural integrity. CLARITY delivers more than beautiful high-resolution images, says Kim. It allows scientists to extract quantitative data from intact biological systems, which leads to meaningful discoveries. Kim and his colleagues have also implemented a novel method they are calling eTango, which drastically accelerates antibody staining processes that enable scientists to label targeted neurons for manipulation and analysis. Members of the Chung Lab will continue to use these innovative technologies to further probe the complex underlying structures of brain functionality and disease.




## Invariant Representations for Action Recognition in the Human Visual System

LEYLA ISIK, POGGIO LAB (MCGOVERN INSTITUTE)

When you walk into a meeting, it is important to recognize basic objects, such as the chair you will sit in, but it is also critical to note the actions of others, so you don't sit in the same chair as another person, for example. Most visual neuroscience and computer vision studies focus on the recognition of static objects, but the ability to recognize dynamic actions is critical to scene understanding and social perception. Using human neuroimaging (MEG), machine learning and a biologically inspired computer vision system, graduate students Leyla Isik and Andrea Tacchetti tested what happens when an actor or viewpoint transforms the visual appearance of an action.

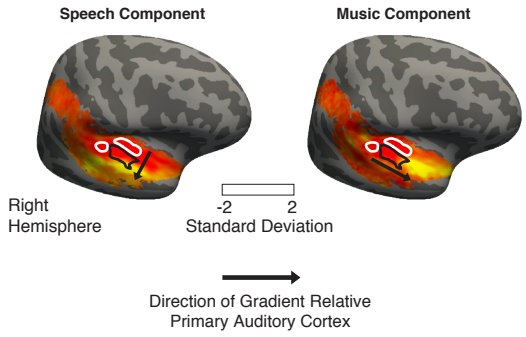


They found neural representations for action recognition that were able to discriminate between different actions, while still being able to generalize across these transformations. This translates into actions being recognized within a few hundred milliseconds, regardless of actor or viewpoint. They are now working on a computational algorithm to model these phenomena.

## Responses to Natural Sounds Reveal the Functional Organization of Human Auditory Cortex

SAM NORMAN-HAIGNERE, MCDERMOTT/KANWISHER LABS (MCGOVERN INSTITUTE)

The part of the brain responsible for hearing supports an impressive range of perceptual abilities that we typically take for granted: we are able to recognize different patterns of speech, perceive and appreciate music, and recognize many other types of sounds in our environment. However, unlike the visual cortex, there is limited consensus among neuroscientists about how auditory cortex is organized. Graduate student Sam Norman-Haignere and his colleagues addressed this question by measuring responses throughout human auditory cortex to a diverse collection of natural sounds that people regularly encounter in daily life. The results of this experiment have provided some of the first evidence that the human brain contains distinct pathways that are specialized for processing speech and music respectively.




## Activity-Dependent Translation of Neurogranin in Hippocampus Is Important for Contextual Memory Formation

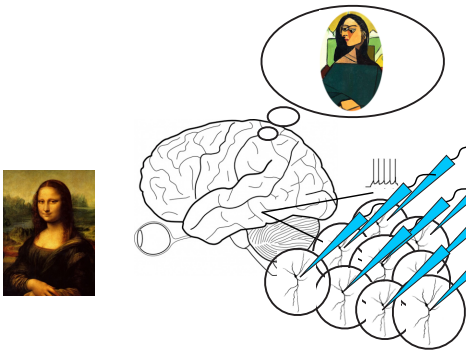
KENDRICK JONES, XU LAB, (PICOWER INSTITUTE)

Understanding how memories are formed is of keen interest to the members of MIT's neuroscience community at this year's retreat. It is well understood that calcium levels mediate essential neuronal functions that impact the strength, or plasticity, of the brain's synapses. Postdoctoral fellow Kendrick Jones talked about neurogranin, a brain-specific protein molecule that regulates calcium-dependent events by modulating the availability and dynamics of calcium-binding protein calmodulin. In previous studies, scientists revealed that neurogranin levels in the hippocampus positively correlate with contextual learning and memory formation. In more recent studies, researchers found that neurogranin levels are rapidly regulated by experience in hippocampus, a brain structure critical for memory formation. Moreover, elevated neurogranin levels facilitate synaptic plasticity and learning. Jones and others believe fluctuations in the amount of neurogranin can alter the calcium dynamics that influence brain plasticity.

## Optogenetic and Pharmacological Suppression of Face-Discriminatory Neural Clusters Reveals their Causal Role in Face Discrimination Behavior

ARASH AFRAZ, DICARLO LAB (MCGOVERN INSTITUTE)

Why and how do we consistently recognize the infamous face of the Mona Lisa? Nearly thirty years ago, it was discovered that specific neurons, organized in clusters in the monkey inferior temporal (IT) cortex, respond selectively to faces. However, most of the evidence related to these neurons involved in face recognition has been correlational rather than causal, in other words we don't know yet if these neurons are causally supporting face discrimination or their responses are epiphenomenal. Arash Afraz and colleagues are studying the perceptual consequences of artificial perturbation of the spiking activity of IT neurons. They are investigating how do populations of neurons in IT cortex causally support visual object recognition (including face recognition). They use face-selective neurons as a proxy to begin this investigation because face-selective neurons are spatially clustered and easy to target experimentally. Afraz's experiments show that when face-selective neurons are inactivated (via drug microinjection also by shining light into the brain tissue in an optogenetic preparation), the ability to identify the gender of a face is diminished. The gender identification deficit happens only in the visual hemifield contralateral to the targeted brain hemisphere and the size of the deficit corresponds to the amount of inactivated brain tissue. Afraz and colleagues in DiCarlo lab view these results as a small but important step towards characterization of the causal role of IT neurons in object recognition.



*How does activation of inferotemporal neurons constrain perception of visual objects?*

## Creation of Versatile AAV-Based Activity Reporters

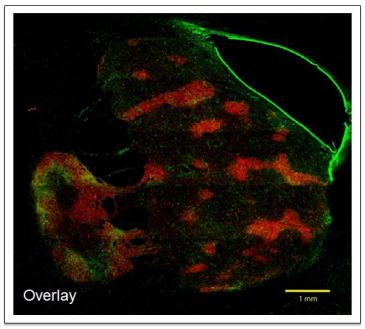
ANDREAS TOFT SØRENSEN, LIN LAB (MCGOVERN INSTITUTE)

Postdoctoral associate Andreas Sørensen presented exciting data from the Lin lab, beginning and ending his presentation with the hope that the tool his research team implemented can be leveraged by others in the MIT neuroscience community. Following up on work initiated by graduate student Kartik Ramamoorthi, Sørensen's team developed a Robust Activity Marking (RAM) tool that can genetically tag recently activated neurons—connected in "active neuronal ensembles"—that are responsible for encoding learned behaviors. The tool's advanced capability allows scientists to simultaneously manipulate cells and measure neural activity that regulates gene expression in transgenic mice. Sorensen emphasized the system's modularity. Its versatility across multiple species and brain regions makes it compatible with a broad variety of experimental designs and demands.

## A Cortico-Striatal Circuit that Controls Approach-Avoidance Behaviors

SATOKO AMEMORI,
GRAYBIEL LAB (MCGOVERN INSTITUTE)

So many in our society suffer from depression and anxiety disorders. Postdoc Satoko Amemori and her colleagues are studying the neuronal mechanisms of these psychiatric diseases in monkeys since their brain structures are so similar to ours. Reinforcing the finding that humans with anxiety tend to choose avoidance when presented with an opportunity to approach or avoid conflict, monkeys receiving anti-anxiety medication are more likely to address conflict. Previous studies revealed that two specific regions of the brain are related to mood and anxiety disorders. Furthermore, striosomes in the brain's striatum receive input from these particular regions. Amemori's team has demonstrated that circuits connecting the two regions to the striatum contribute to pessimistic evaluation in approach-avoidance decision making, suggesting that this interactive pathway may be crucial for regulating mood and anxiety disorders.

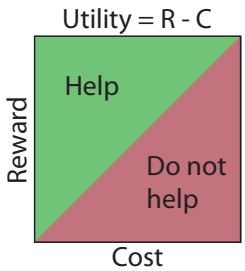



*Striosomes (red regions) receiving inputs (tagged by green fluorescent) from anxiety-related cortex.*

## Social Evaluations and the Naïve Utility Calculus

JULIAN JARA-ETTINGER, SCHULZ LAB
(DEPARTMENT OF BRAIN AND COGNITIVE SCIENCES)

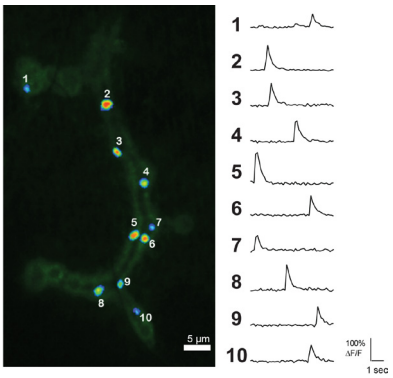
Even babies think about other people's behavior in terms of goals. If they see an adult reach for a toy bear, for example, they expect the adult to continue reaching for the same toy, even if it's position changes. Humans are able to infer the goals of others based on the assumption that they behave efficiently. However, understanding goals will only take you so far. Fortunately, children as young as two years old possess a level of sophistication that allows them to reason about how rewards and costs impact actions taken to reach goals, and they can use this information to make social evaluations. For example, kids will excuse an adult for refusing to help with a task due to incompetence, but not merely lack of motivation. Graduate student Julian Jara-Ettinger and his colleagues call this the naïve utility calculus because it reflects intuitions emerging in childhood, prior to any formal education.




## Imaging Synaptic Transmission at Individual Active Zones

YULIA AKBERGENOVA,
LITTLETON LAB, (PICOWER INSTITUTE)

Growing neurons in our brain form thousands of synapses through which critical information is communicated to target cells. Changes in synapse strength, likely mediated by vesicle fusion in the active zones of these synapses, impact brain development and plasticity. Postdoctoral fellow Yulia Akbergenova and her team generated a new technique to measure the fusion of individual synaptic vesicles in a single active zone and thereby characterize how specific release sites transmit information. Using the toolkit they developed, researchers found high variability in both evoked and spontaneous fusion across active zones, indicating a variety of possible mechanisms responsible for regulating synaptic plasticity. They also discovered a subset of active zones associated with only the spontaneous mode of release, suggesting the possibility of unique information pathways in these particular synapses.

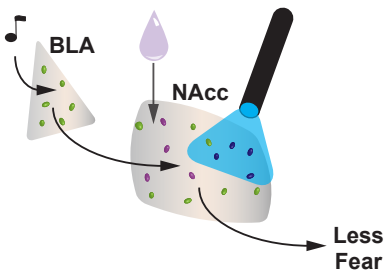



*The fluorescent Ca2+ sensor myrGCaMP5 is expressed postsynaptically at the Drosophila NMJ.*

## An Amygdala-Nucleus Accumbens Circuit Regulates the Persistence of Fear Extinction

SUSANA CORREIA,
GOOSENS LAB (MCGOVERN INSTITUTE)

Every year, nearly 9 percent of adults experience some kind of phobia. Postdoctoral fellow Susana Correia is interested in studying extinction of fear because the failure to extinguish fear and fear return are defining features of emotional disorders characterized by exacerbated fear. Treatments based on exposure therapy—introducing fearful stimuli to subjects in a safe environment—help patients adopt useful coping mechanisms. However, while this treatment approach is highly effective for phobias, it is successful in only about half of PSTD cases.




*Tone-reward association (which activates the BLA-NAc circuit) or optogenetic activation of the BLA-NAc circuit during fear extinction reduce fear memory return.*

Correia used rats to experiment with fear extinction as a model for exposure therapy. She and her colleagues hypothesize that if the timeline for fear extinction is extended, the efficacy of treatments like exposure therapy will improve. To accomplish this they delivered a reward sweet solution to rats during extinction of fear and found that this procedure reduces the persistence of fear and also increases activity of neurons in the circuit connecting the amygdala region of the brain to the nucleus accumbens. They also found that optogenetic activation of this circuit during fear extinction reduces the likelihood the fear will return.

## Carving Nature at its Joints: From Associative Learning to Visual Perception

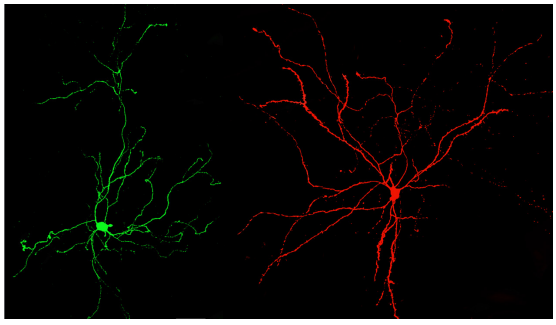
SAM GERSHMAN, TENENBAUM LAB
(DEPARTMENT OF BRAIN AND COGNITIVE SCIENCES)

Why do we not see the world's complex myriad of events, objects, people, and places as mass confusion? A central task of cognitive science is understanding how we process all these undifferentiated sensory inputs into a coherent perceptual experience, says postdoc Sam Gershman. Discovering more about how these underlying structures work provides insights about associative learning and decision-making processes. Gershman and Josh Tenenbaum believe there are common computational principles operating across various domains. They are studying motion perception and using it as a foundational model to gain a better understanding of the structural interpretations we extract from sensory data.

## A Circuit Mechanism for Differentiating Positive and Negative Associations

PRANEETH NAMBURI, TYE LAB, (PICOWER INSTITUTE)

Valence is the intrinsic attractiveness or aversiveness of an event, object, or situation. For instance, when PhD candidate Praneeth Namburi was growing up in India, he remembers the sound of two bells on the school speaker signaling the dreaded morning assembly, whereas multiple bells announced recess. So several rings resulted in positive valence for most kids, especially Praneeth, who says he is not a "morning person." About half of the more than one hundred thousand neurons in the brain's basolateral amygdala encode valence, with some focusing on the positive while others concentrate on the negative. Using a mouse model and Pavlovian conditioning tasks, Namburi and his collaborators have identified a divergence in the neural circuits encoding positive and negative valence.



*Representative neurons in the Basolateral Amygdala (BLA) that are involved in encoding positive and negative valence.*

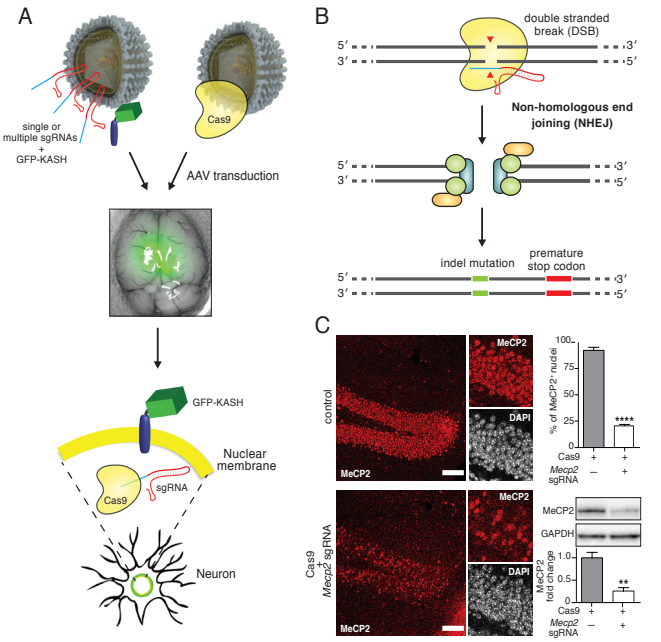
PRESENTATION

# WINNER

## In Vivo Interrogation of Gene Function in the Mammalian Brain Using SPCas9

MATTHIAS HEIDENREICH,
ZHANG LAB (MCGOVERN INSTITUTE)

With its intricate system of numerous interconnected networks and regions, the brain remains the most complex and least understood organ in the human body. We do know that a functional nervous system—responsible for information processing and higher cognitive functions like learning and memory—relies on the proper organization of neuronal circuits that fine-tune activity in the brain's networks. This structure can be manipulated through genomic engineering, but new technologies are needed to help scientists more efficiently and precisely alter the genome to enhance understanding of neuronal circuitry. Postdoctoral fellows Matthias Heidenreich and Lukasz Swiech have devised an economical and flexible approach for use in animal models—a promising technology that enables simultaneous targeting and modification of multiple genetic elements, producing a variety of biochemical, molecular, and behavioral phenotypes.




*CRISPR/Cas9 mediated genome editing in the mammalian brain: A) Adeno-associated virus (AVV) mediated co-delivery of single guide RNAs (sgRNAs) and the nuclease Cas9 into the mouse brain. Visualization of targeted neurons by a fluorphor (GFP-KASH) integrated into the nuclear membrane. B) sgRNA guided induced double strand brake results in indel mutations and premature stop codons in the targeted gene. C) Cas9 mediated knock down of the protein MeCP2 in the mouse hippocampus 4 weeks after virus delivery.*

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# Neuroscience News // Summer 2014

**TOP ROW:**: MARK F. BEAR, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Investigator, Howard Hughes Medical Institute (HHMI); KWANGHUN CHUNG, Assistant Professor, Departments of Chemical Engineering and Brain and Cognitive Sciences. 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.
**MIDDLE ROW:** EARL MILLER, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences; 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.
**BOTTOM ROW:** 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.

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