Picower Institute for Learning and Memory

The Picower Institute for Learning and Memory is a community of scientists dedicated to understanding the mechanisms that drive learning and memory and related functions such as cognition, emotion, perception, and consciousness. Picower Institute researchers explore the brain at multiple scales—from genes and molecules, cells and synapses, to circuits and systems—producing novel insights into how disruptions in these mechanisms can lead to developmental, psychiatric, or neurodegenerative disease.

Awards and Honors

Mark Bear: 2018 Beckman-Argyros Vision Research Award

Emery Brown: Elected a member of the Florida Inventors Hall of Fame; served as interim director of the Institute for Medical Engineering and Science

Myriam Heiman: Department of Brain and Cognitive Sciences (BCS) award for Excellence in Graduate Mentoring

Troy Littleton: BCS departmental award for Excellence in Graduate Teaching; co-organizer, Neurobiology of *Drosophila* meeting at Cold Spring Harbor

Elly Nedivi: BCS departmental award for Excellence in Undergraduate Teaching

Mriganka Sur: Doctor of Science *honoris causa*, Indian Institute of Technology, Kanpur

Kay Tye: National Institutes of Health Director's Pioneer Award; departmental award for Excellence in Postdoctoral Mentoring

Alyssa Dayan (Flavell Lab undergraduate): Randolph G. Wei Undergraduate Research Opportunities Program Award

Dustin Hayden (Bear Lab graduate student): Angus MacDonald Award for Excellence in Undergraduate Teaching.

Ni Ji (Flavell Lab postdoctoral fellow): Charles King Trust Postdoctoral Fellowship

Fergil Mills (Tye Lab postdoctoral fellow): Brain Star Award from Canadian Institutes of Health Research

Marvin Nayan (Sur Lab graduate student): Department of Biology award for Graduate Teaching

Amanda Vernon (Heiman Lab graduate student): BCS departmental teaching award

Joyce Wang (Tye Lab graduate student): BCS Departmental teaching award

Research Advances

Members of the laboratories of Picower Institute faculty made a number of major research advances during academic year 2018.

Researchers in the Mark Bear Lab made several key discoveries. They showed that selective inhibition of glycogen synthase kinase alpha corrects a broad range of fragile X phenotypes in mice. The alpha-selective inhibition avoids the toxicity associated with inhibitors that act on both alpha and beta paralogs, opening the door to a completely novel class of therapeutics for fragile X and related disorders. Researchers also showed that dendritic spine shrinkage in response to glutamate is no longer regulated by protein synthesis in fragile X model mice. Spines receive excitatory synapses and are known to have an aberrant morphology in fragile X, but how this arises has been unknown. This work revealed an unexpected role for signaling downstream of the N-methyl-D-aspartate–type glutamate receptor in the pathophysiology of fragile X. Other work in the Bear laboratory built on an earlier discovery that amblyopia can be completely reversed by temporary inactivation of the retinas. This effect was observed even after inactivation of only one retina, bringing closer the day when this approach can be translated into the clinic. A start-up company has been formed to pursue this approach clinically.

Members of the Emery Brown Lab reported the development of highly efficient algorithms to perform real-time denoising and high-resolution spectral analysis of time series. They developed a new, coherent theory for administering general anesthesia, termed multimodal general anesthesia. It uses multiple anesthetics to control pain at multiple sites, thereby significantly reducing opioid administration and the quantity of anesthetics producing unconsciousness, and, as a consequence, postoperative brain dysfunction.

The Myriam Heiman Lab identified the striatal-enriched transcription factor Foxp2 as an important regulator of Huntington's disease–associated phenotypes. Researchers also showed that chronic dosing of the anti-psychotic drug clozapine enhances glutamatergic drive to the ventral striatum, a region of the brain previously implicated in schizophrenia.

Members of the Troy Littleton Lab performed a detailed structure-function analysis of the synaptic vesicle calcium ion (Ca^{2+}) sensor synaptotagmin 1 to determine how it regulates neurotransmitter release. Synaptotagmin acts as a fusion trigger by binding calcium ions at the base of its two C2 domains that drive interactions with membrane lipids. Beyond membrane insertion by the C2 domains, other requirements for synaptotagmin function have been poorly understood. To dissect the protein further, researchers took advantage of recent observations that mutations in the Ca^{2+}-binding pocket of the C2B domain of synaptotagmins dominantly disrupt vesicle fusion from invertebrates to humans. They performed an intragenic screen for suppressors of the lethality induced by expression of synaptotagmin C2B mutants in *Drosophila*. They uncovered 20 essential residues within synaptotagmin that are required for the dominant-negative activities of the mutant C2B protein. These residues map to distinct regions and suggest a structural basis for several synaptotagmin activities required for vesicle release. Their data indicate that intra-domain C2A-C2B interactions, the C2B polybasic region, and synaptotagmin dimerization are required for promoting normal amounts of vesicle fusion but are not absolutely critical for the timing of vesicle exocytosis. In contrast, they found that a distinct C2B surface opposite the polybasic stretch that SNARE complex interactions were required for rapid synchronization and Ca^{2+} cooperativity of vesicle release. Using electrophysiological, morphological, and computational characterization of these mutants, they proposed a sequence of molecular

interactions mediated by synaptotagmin 1 that promote Ca^{2+} activation of the synaptic vesicle fusion machinery and subsequent neurotransmitter release.

Lab members also found that synaptic pathology and lethality were linked to perturbations of endosomal trafficking in a *Drosophila* Huntington's disease model. Pathogenic Huntingtin (Htt) disrupts multiple neuronal processes, although the primary pathogenic mechanism and subcellular site of action for mutant Htt are still unclear. They observed that pathogenic Htt expression leads to a profound overgrowth of synaptic connections that directly correlated with the levels of Htt at nerve terminals. Branches of the same nerve containing different levels of Htt showed distinct phenotypes, indicating that Htt was acting locally to disrupt synaptic growth. The effects of pathogenic Htt on synaptic growth arose from defective synaptic endosomal trafficking, leading to expansion of a recycling endosomal signaling compartment and a reduction in late endosomes. The disruption of endosomal compartments resulted in elevated bone morphogenetic protein (BMP) signaling within nerve terminals, driving excessive synaptic growth. Blocking aberrant signaling from endosomes or reducing BMP activity ameliorated the severity of Huntington's disease pathology and improved viability. These data indicate that pathogenic Htt acts locally at nerve terminals to alter trafficking between endosomal compartments, leading to defects in synaptic structure that correlate with pathogenesis and lethality in the *Drosophila* Huntington's disease model.

Members of the Earl Miller Lab published several experimental and theoretical papers suggesting a new model of working memory, the sketchpad of consciousness. Their research suggests that interplay between different cortical rhythms, beta (10–30 Hz) and gamma (30–100 Hz), in different cortical layers, allow volitional control over what is held in mind—in other words, an infrastructure for controlling our own thoughts. This is the first theory or model of its type and it is gaining attention.

Miller Lab researchers published a paper showing, for the first time, how sensory inputs are gradually transformed across the cortex into meaningful knowledge. They also showed how different cortical rhythms underlie different styles of learning—a cognitive (explicit) or automatic, "muscle-memory" (procedural) style. Even though 60,000 people a year in the United States alone undergo general anesthesia, no one knows how it renders people unconscious. In collaboration with the Emery Brown Lab, the Miller Lab is conducting the first wide-ranging assessment of the effects of general anesthesia on cortical neurons and networks. This includes testing the hypothesis that deep brain stimulation can wake an animal from general anesthesia.

The Elly Nedivi Lab continued its work on bipolar disorder, a common mood disorder characterized by recurrent episodes of mania and depression. Both genetic and environmental factors have been implicated in the etiology of bipolar disorder, but the biological underpinnings have remained elusive. Recently, genome-wide association studies of neuropsychiatric disorders have identified a risk locus for bipolar disorder containing the *SYNE1* gene, a large gene encoding multiple proteins. The association signal almost exclusively spans the part of *SYNE1* encoding CPG2, a brain-specific protein localized to excitatory postsynaptic sites where it regulates glutamate receptor internalization. The Nedivi Lab recently showed that CPG2 protein levels are significantly decreased in postmortem brain tissue from patients with bipolar disorder compared with

control subjects, as well as in patients with schizophrenia and depression. They identified genetic variants within the postmortem subjects that map to the CPG2 promoter region and negatively affect gene expression, as well as mis-sense single nucleotide polymorphisms in CPG2 coding regions that affect CPG2 expression, localization, and synaptic function. These findings link genetic variation in the CPG2 region of *SYNE1* with a mechanism for glutamatergic synapse dysfunction that could underlie susceptibility to bipolar disorder in some individuals. Few genome-wide association studies in human genetics for neuropsychiatric disorders to date have afforded such mechanistic clues. Further, the potential for genetic distinction of susceptibility to bipolar disorder from other neuropsychiatric disorders with overlapping clinical traits holds promise for improved diagnostics and treatments of this devastating illness.

Researchers in the Bear Lab made recordings of visually evoked potentials that showed that aging-related interneuron dendritic arbor simplification and reduced dynamics go hand in hand with the loss of induced stimulus-selective response potentiation, a paradigm for adult visual cortical plasticity. Chronic treatment with the antidepressant fluoxetine reversed deficits in interneuron structural dynamics and restored stimulus-selective response potentiation in aged animals. These results support a structural basis for age-related impairments in sensory perception and suggest that declines in inhibitory neuron structural plasticity during aging contribute to reduced functional plasticity.

The Mriganka Sur Lab achieved three research advances in academic year 2018. First, they discovered a fundamental rule by which synaptic connections change to exhibit plasticity of neuronal responses during development or learning. Using advanced imaging techniques, they showed that when one synapse strengthens, immediately neighboring synapses weaken. These changes happen because of the action of one critical protein, the activity-regulated cytoskeleton-associated protein (Arc).

Second, they provided evidence that the brain region called the posterior parietal cortex (PPC) plays a key role in converting vision into action. Employing a series of behavioral tasks and 2-photon imaging of neuronal responses across cortical regions in awake mice, they showed that distinct sets of neurons in PPC are involved in visuomotor transformations.

Third, they revealed a new mechanism for an autism-related gene in brain function, showing that the gene MVP, which encodes major vault protein (MVP) and is a candidate gene in 16p11.2 microdeletion syndrome—one of the most common genetic causes of autism—is an important regulator of plasticity via its influence on signal transducer and activator of transcription 1 (STAT1) and extracellular signal-regulated kinase (ERK) signaling. This study suggests a broader role for neuroimmune interactions in circuit-level plasticity and in the mechanisms of autism.

Researchers in Susumu Tonegawa's laboratory characterized distinct neuronal pathways for memory formation and retrieval. They found a distinct role of the dorsal subiculum in retrieval memory. The CA1–dorsal subiculum–medial entorhinal cortex layer five circuit played a crucial role in the retrieval of episodic memories, but not in their formation. Conversely, the CA1–medial entorhinal cortex–layer five circuit was essential for memory formation, but not retrieval.

Tonegawa Lab members demonstrated direct functional relationship between specific hippocampus neurons and the medial entorhinal cortex in memory replay. They showed that ripple bursts in CA1 and the medial entorhinal cortex are temporally associated, and that medial entorhinal cortex III input to CA1 is crucial for ripple bursts and long-range replays, specifically in the quiet awake state. CA3 input is essential for both, regardless of behavioral state.

Researchers also showed that dorsal raphne serotonergic neuronal input to the nucleus accumbens plays an important role in brain processes evaluating delayed reward. They found that augmentation or reduction of dorsal raphne serotonergic neuron activity during decision making was sufficient to influence an animal's impulse for an immediate or a delayed reward.

A specific pattern of connectivity between engram cell ensembles, rather than a specific pattern of strengthened synapses, was found to be crucial for memory storage. Laboratory members found that engrams incapable of eliciting memory by natural recall cues—due to low synaptic strength—were nonetheless sufficient for optogenetic recall for up to eight days following an experience.

Researchers in the Tonegawa Lab also demonstrated that the locus coeruleus area of the brain is important in memory formation and retrieval. They showed that this area of the brain plays a crucial role in signaling novelty that supports immediate memory formation after a one-time experience. Specifically, locus coeruleus neuromodulation to the CA3 brain region was found to be necessary for memory formation; without this, memory retrieval was weakened and imprecise.

In the Li-Huei Tsai laboratory, in collaboration with Ariv Regev at the Broad Institute, researchers employed the technique of gene expression profiling in single cells to study the population heterogeneity and the emergence of distinct subtypes of microglia, the brain macrophages, in response to neuronal death in a mouse model of severe neurodegeneration. Researchers also applied the technologies of genome editing with the CRISPR/Cas9 tool to induced pluripotent stem cells (iPSC) to generate genetically identical iPSC lines harboring either the common ApoE3 allele or the ApoE4 allele. The ApoE4 allele confers the single greatest known risk for developing late-onset Alzheimer's disease. These iPSC lines made it possible to discover how possessing ApoE4 could affect the development of Alzheimer's disease–related pathologies in various iPSC-derived neurons and non-neuronal cell types.

A postdoctoral associate in the Kay Tye Lab, Nancy Padilla, developed a modified cage system (a minivivarium) to simplify housing animals in groups of eight to 10. This is the first prototype of scaling-up the housing of mice to vivarium size, with the ability to track social behaviors while simultaneously recording and manipulating neural circuits in real time during natural (social) behaviors. This offers the opportunity to test and compare new cutting-edge imaging and recording techniques and to assess whether they can be scaled up to recording from 20 to 30 animals in a large vivarium structure.

Padilla also set up a novel trial-based behavioral paradigm that enables neural recordings of multiple mice while taking social rank into account. These developments have a pivotal role in allowing the establishment of a completely new research direction in the lab, encompassing larger social groups, social rank, and the neural circuits underlying social behaviors and development and representation of rank.

Members of the Tye Lab recently showed that the transfer of neuronal signals from social cues from cortical neurons to the basolateral amygdala plays a critical role if observational fear learning is to occur. Researchers demonstrated that the neurotransmitter dopamine increases the signal-to-noise ratio of responses to aversive stimuli in medial prefrontal cortex that project to the dorsal periaqueductal gray.

The Weifeng Xu Lab reported discoveries in the area of signaling scaffold for excitatory synapses. The specificity of signal transduction from neurotransmitter release to intracellular signaling cascades is critical for information encoding in the brain. Synaptic scaffold proteins orchestrate the signal transduction through organizing different protein networks. Researchers investigated how different scaffold proteins regulate excitatory synaptic transmission using virus-mediated molecular manipulation. They also illustrated the functional specialization among different families of scaffold proteins and different members of the same family of proteins in terms of interaction with neural activity and interaction with different neurotransmitter receptor complexes. With the Xu Lab's efforts in cutting-edge quantitative proteomics and phosphoproteomics, these findings provide a comprehensive view of the signaling networks and molecular mechanisms important for experience-dependent modification of synaptic connectivity. The protein PSD-95 controls postsynaptic ubiquitination and phosphorylation signaling pathways.

Rapid, experience-dependent translation of neurogranin enables memory encoding. Calcium is essential for activity-dependent neural plasticity in the brain. The cellular response from calcium influx is normally mediated by processes dependent on the calcium-binding protein calmodulin. Researchers identified neurogranin, a neuronal calmodulin-binding protein associated with schizophrenia and mental retardation that is rapidly translated on novel context exposure and is required for memory formation. Fragile X mental retardation protein interacts with neurogranin and is required for activity-dependent translation of neurogranin in the synaptic compartment and contextual memory formation. Researchers found that adrenergic signaling is involved in novel-context-induced neurogranin translation, facilitation of protein synthesis–dependent long-term potentiation, and memory formation, and that enhancing adrenergic signaling can rescue memory deficit caused by fragile-X mental retardation protein deficiency. These findings illustrate molecular mechanisms important for memory formation and provide potential therapeutic targets for autism spectrum disorders.

Personnel

More than 264 community members participated in Picower Institute activities during the academic year: 14 faculty members, three visiting scientists or scholars, 73 postdoctoral associates, 28 research scientists, 47 undergraduates, 35 graduate students, 28 research and technical staff, and 16 administrative and service staff.

Items of note during the academic year included the following:

- William Lawson was hired as assistant director for administration in January 2018, replacing Erin Edwards.
- Arlene Heywood-Dortch was hired as a financial assistant in March 2018, replacing Tracy Nash.

- Renee LeBlanc was hired as senior financial officer in October 2017, replacing John Maher.
- Kwokin Ou was hired as financial coordinator in September 2017, replacing April London.
- David Orenstein was hired as director of communications in December 2017.
- Demetria Gordon was hired as an administrative assistant to Kay Tye and Steve Flavell in October 2017, replacing Jean Achorn.
- Jessica Buckey was hired as an administrative assistant to Mark Bear in January 2018, replacing Nina Palisano.
- Eileen Oelhaf was hired as a temporary development administrative assistant to Asha Bhakar in August 2018, replacing Tania Kyle.
- Meredith Mahnke became to laboratory manager in Earl Miller's lab.

Resource Development

The Picower Institute has enjoyed impressive success over recent years and that trend continued in fiscal year 2017. Picower resource development efforts identified and publicized more than 180 collaborative funding opportunities, extended the print newsletter outreach to 2,393 individuals worldwide, hosted visits with more than 70 prospective and current donors, and, with help from the communications director, worked closely with Picower faculty members to draft seven prize nominations and 24 new formal philanthropic proposals. Outright gift payments to the Picower Institute for FY2017 totaled more than $10.9 million; new philanthropic gifts and pledges totaled more than $24.2 million.

Due to the generous support of the JPB Foundation, Barbara Picower, and the late Jeffry Picower, researchers at the institute have continued their ambitious efforts. Four new gift commitments totaling $18,300,000 supported the renewal of the Picower Institute Innovation Fund (PIIF), a new Picower Fellows Program, planned work in Susumu Tonegawa's laboratory, and completion of the Junior Faculty Development Program (JFDP). The PIIF is the Picower Institute's flagship program to empower the institute's scientists to take risks as they conduct research into the challenges and mysteries of neuroscience. To date, the PIIF has brought in over $44.7 million in grant funding to the institute, generated more than 167 publications, launched three companies, and has been the basis for global collaboration. The Picower Fellows Program developed a formal trainee structure to support the recruitment and retention of postdoctoral scientists. To date, this program has supported 33 individuals, including 22 international scholars, 13 female scientists, and two members of underrepresented minority groups. JFDP provides mentoring and career development support to junior faculty; this year's gift provided support for the newest faculty member, Steve Flavell, for use in his fifth and sixth years at MIT-a critical time in a junior faculty member's progression to tenure.

In FY2017, all JPB-supported institute programs—PIIF, the Picower Fellows Program, JFDP, and the Catalyst Program—supported breakthroughs in better mapping of the

brain in three dimensions, in understanding how synapses encode information we learn, and in identifying brain circuits and disruptions that are key to various brain illnesses. Investing in this basic research has the potential to save lives and result in direct and indirect economic impact.

Significant efforts and development resources have continued to be directed toward the Aging Brain Initiative, a major cross-institutional health research initiative on brain aging and related cognitive decline. Picower Institute director Li-Huei Tsai leads this effort, along with Dean Michael Sipser of the School of Science and seven founding faculty members from different disciplines across MIT. It remains a top health priority in MIT's Campaign for a Better World. Major events to raise awareness and increase the visibility of the effort this past fiscal year included an MIT Campaign roadshow held in Boston and two breakfast events hosted by unaffiliated donor and supporter Alan Patricof at Greycroft Partners in New York City. The breakfasts connected the institute's efforts with several influential individuals from New York, some of whom have since visited campus to see the initiative's work firsthand and made gifts to support the research. The Aging Brain Initiative also sponsored its first scientific symposium, Brain Rhythms in Health and Disease, which drew a standing-room-only audience at the Picower Institute on April 4.

Notable new commitments in support of the Aging Brain Initiative include a generous $1.5 million pledge from the Robert A. and Renee E. Belfer Family Foundation. The gift supports research into how to effectively translate the Picower Institute's noninvasive Alzheimer's research into clinical use. The Belfer family also continued support for other breakthrough research through the Belfer Neurodegeneration Consortium—a collaborative enterprise comprising scientists from MIT, the University of Texas MD Anderson Cancer Center, Baylor College of Medicine, and Mount Sinai School of Medicine. This funding enables investigation into ways to slow, stop, or reverse the progression of Alzheimer's disease with the goal of identifying and developing new therapeutic targets.

New six-figure gifts and pledges from the Eleanor Schwartz Charitable Foundation, Alan Patricof, MIT alumni Lester Gimpelson ('57), Jean-Jacques Degroof ('93), Margaret Ridge-Pappis ('59), the Hahn Family ('90), and David Emmes ('76) provided an additional $2.4 million in funds to defray many of the costs of effectively translating noninvasive light and sound therapy for human use in Alzheimer's disease. The Ludwig Family Foundation renewed its support for Picower's efforts to map the aging brain in collaboration with MIT bioengineering professor Ed Boyden. Moreover, several formal proposals have been developed to expand the initiative's efforts in mitigating the effects of Down syndrome, amyloid lateral sclerosis (ALS), Parkinson's disease, and traumatic brain injury.

The Picower Institute hosted its biannual spring symposium, Early Life Stress and Mental Health, in honor of guest and generous donor, Barbara Picower. The event took place on May 9 and featured talks and panel discussions among high-profile neuroscientists, psychologists, physicians, journalists, educators, policy experts, and parents. Speakers examined how experience and biology combine to affect the development and outcomes of young minds. The event was well attended (with approximately 470 registrants). Through compelling personal stories and research evidence, speakers showed that by combining science and activism people can make progress in helping children survive toxic stress.

This past year, the Picower Institute also received a $1.5 million bequest intention from MIT alumnus Donald Mattes ’67 and his wife Glenda. Donald and Glenda have been supporting work at the institute with annual donations over several years, with a particular interest in work on Alzheimer’s disease. Additionally, the number of five-figure and smaller annual fund gifts from dedicated donors has more than tripled this year.

Media Recognition

During AY2018, Picower Institute faculty members published 74 articles. They appeared in such hallmark journals as *Science*, *Neuron*, *Cell*, *Cell Reports*, *Nature Communications*, and *Proceedings of the National Academy of Sciences*.

The Picower Institute and MIT’s news office issued 23 institute-related press releases during the reporting period. Various news sources reported on Picower research and news on institute research and faculty members appeared in major media outlets such as *Wired*, *Scientific American*, Fast Company, *Forbes*, *Science News*, the *Scientist*, the *Boston Globe*, *Nature*, the *Atlantic*, *Smithsonian*, *The Guardian*, *The Week*, CBS Boston, Inc., *Redbook*, *Cosmopolitan*, Vice.com, *Quanta Magazine*, Stat, the *Daily Mail*, the Daily Beast, and Xinhua, the official Chinese news outlet.

Programs and Activities

The Picower Institute was founded on the premise that collaboration among disciplines is an integral component of its research philosophy. To facilitate these interactions, the Picower Institute plans a rigorous calendar of formal lectures, conferences, and workshops, as well as other informal events each year. Activities are designed to bring Picower researchers and the MIT neuroscience community together with other neuroscientists and practitioners from the public and private sectors to exchange research findings, facilitate cross-disciplinary collaborations, and continue to explore the potential that research advances about learning and memory mechanisms in the brain offer to science and society. Ongoing programs and activities are described below.

The Picower Institute Colloquia bring together learning and memory researchers from universities throughout the world to share their findings and experiences with the MIT community and to create working relationships with members of the Picower Institute. During the past year, colloquia speakers included Joshua Johansen and Hokto Kazama of the RIKEN Brain Science Institute, Tony Wyss-Coray of Stanford University, Cyril Herry of the University of Bordeaux, David Lewis of the University of Pittsburgh, and Mark Andermann of Beth Israel Deaconess Medical Center and Harvard Medical School.

In the language of neuroscience, “plasticity” refers to the minute but crucial physical changes that take place in our synapses every time we learn, experience, or remember anything new. At the Picower Institute, “Plastic Lunch” refers to a monthly series of informal talks during the academic year that give postdoctoral associates and graduate students from across the institute a chance to share their latest research with colleagues within the Building 46 community. The Plastic Lunch series provides an opportunity for participants to improve their presentation skills; it also fosters collaborations and builds new relationships across disciplines and between labs.

Picower Power Lunches also continued to be held throughout the academic year. These are monthly faculty lunches that allow faculty and guest speakers to relate recent research findings or present a new idea informally.

The Picower Institute hosted its annual fall symposium on October 13, 2017. The topic was neural circuits of motivation and emotion. Experts from around the globe came to share their latest research findings relating to the neural circuits of reward-seeking behavior, homeostasis, fear learning, exploration, and social behavior. The event was well attended, with more than 500 registrants.

Held annually, the Picower Lecture was named to honor and recognize the generous support of the Picower Foundation for neurosciences at MIT. Each lecture features the work of a contemporary leader in the area of brain research. This year's lecturer was Fred "Rusty" Gage of the Salk Institute for Biological Studies, winner of the Christopher Reeve Research Medal and the Max Planck Research Prize. He spoke at the Picower Institute on October 16, 2017.

Together with the School of Science, the Picower Institute continued the newly launched Aging Brain Seminar Series, a bimonthly series focused on fundamental and translational aging brain research. This series has the goal of bringing together bright minds to give idea-focused talks on a wide range of brain-aging subjects to foster learning and inspiration—and to provoke conversations that matter. Speakers included Patrick Purdon of Massachusetts General Hospital and Harvard Medical School, Dr. Richard Ransohoff of Biogen, Dr. Bruce Yankner of Harvard Medical School, and Dr. Scott Small of Columbia University.

The Picower Institute hosted the Aging Brain Initiative's inaugural symposium, Brain Rhythms in Health and Disease, in April 2018. The symposium brought together 11 renowned experts to discuss how neural oscillations coordinate functions such as computation, cognition, learning and memory, perception, and attention. The event saw excellent attendance and drew attendees from institutions from all around the New England area.

The institute also hosted its biannual spring symposium, Early Life Stress and Mental Health, in May. Coordinated with Barbara Picower and her team at the JPB Foundation, this symposium featured talks and panel discussions among neuroscientists, psychologists, physicians, policy experts, and parents examining how experience and biology combine to affect the development of young minds. The event had a large and diverse group of attendees and was also streamed online for viewers throughout the world.

After the close of the academic year, the Picower Institute hosts an annual retreat for its community members. This year, the retreat was held in June in concert with the Department of Brain and Cognitive Sciences and the McGovern Institute for Brain Research. More than 130 Picower Institute members attended the event. The retreat included nine speakers (three from the Picower Institute) as well as 27 posters (12 from the Picower Institute).

The Building 46 Post-Doc Association is an endeavor designed to reach the Picower Institute's postdoctoral community to provide resources and support activities that build community and enrich interactions between postdoctoral colleagues and future associates. The association continues to expand and make improvements for the postdoctoral community in partnership with administrators. Throughout the past year, the association convened a series of informal talks, educational seminars, and social events.

Research programs supported through the JPB Foundation and the RIKEN Brain Science Institute allow the Picower Institute to have a research environment with support for faculty, lab members, and the administrative team. Programs include the Clinical Collaborative Fellowship, the Picower Neurological Disorder Research Fund, the Picower Fellows Program, the Symposium Fund, the Picower Institute Innovation Fund, the RIKEN-MIT Center for Neural Circuit Genetics, and the Catalyst Program.

Research Initiatives

RIKEN-MIT Center for Neural Circuit Genetics

Professor Susumu Tonegawa directs the RIKEN-MIT Center for Neural Circuit Genetics, which was established in April 2008. In April of this year, the RIKEN-MIT research agreement was successfully renegotiated for another five-year period, with continued funding from RIKEN. This renewal was accompanied by a name change; the center will now be known as the RIKEN-MIT Laboratory for Neural Circuit Genetics. Jointly sponsored by the RIKEN Center for Brain Science in Japan and MIT, the laboratory seeks to fully understand the brain mechanisms underlying specific cognitive phenomena such as memory and emotion. Researchers in the lab investigate not only the properties of individual cells, cellular clusters, and brain systems, but also the functions generated by their communications, seeking to uncover the fundamental mechanisms that operate in the healthy brain and to understand how these mechanisms go astray under disease conditions. By combining transgenic and viral vector techniques, in vivo multi-electrode recording technology, optical and magnetic imaging techniques, and behavioral studies, the laboratory follows a highly interdisciplinary approach.

Induced Pluripotent Stem Cell Core Facility

The Picower Institute launched the iPS Core Facility in November 2010. The facility integrates the various research goals of members of the Picower Institute, the McGovern Institute, and the Department of Brain and Cognitive Sciences in an effort to create human and animal cell models of diseases. The various laboratories have expertise and experience with different experimental protocols which, when applied in a collaborative manner to the study of human cells, result in accelerated progress in this field. The advent of human induced pluripotent stem cells (iPSCs) has heralded a new generation of clinical and basic research into human disorders. Patient-derived skin fibroblast cells are reprogrammed into iPS cells, allowing researchers to examine a wide variety of diseases directly in human cells in addition to studying gene variants in patient populations. This core facility has rapidly become essential to studies of autism, psychiatric disease, Alzheimer's disease, and many neurodegenerative diseases. The facility is accessible to users at all hours and shared equipment is available with a reservation system. The iPS facility's doors are also open to other MIT users and to users external to MIT on a fee-for-service basis.

The iPS Core Facility is equipped for the specialized production, maintenance, expansion, preservation, and distribution of human fibroblasts, iPS cell lines, iPS- and embryonic stem (ES)-derived neuronal progenitor cells, iPS- and ES-derived neurons, induced neuronal cells, and neural organoids. The iPS Core Facility has approximately 1,250 square feet of space in three tissue culture areas. One room is dedicated to viral work with iPS and ES cells at biosafety level two plus and two tissue culture areas are for maintenance, expansion, and general handling of nonviral work–related iPS and ES cell cultures at biosafety level 2. There are 10 bio-safety cabinets, 16 carbon dioxide incubators, one three-gas incubator that allows researchers to control of the oxygen concentration, and bench areas. There are also four biosafety cabinets equipped with microscopes for observation and handling of cells in a clean and protected environment. Currently, the iPS Core Facility has produced more than 70 patient-specific iPS cells from donors with schizophrenia, bipolar disease, depression, Rett syndrome, Alzheimer's disease, and Down syndrome, and from healthy donors as controls. The number of cell lines and iPS cells continues to grow.

Tak Ko, the supervisor of the iPS Core Facility, has also set up an orientation program and a number of training sessions to educate faculty and potential users. The iPS Core Facility provides a powerful incentive for different labs to collaborate and exchange ideas. Since its inception, more than 25 researchers at MIT have used the facility, and collaborations with researchers outside MIT have continued, including noteworthy interactions with the Broad Institute. Many papers based on data obtained by using the iPS Core Facility have been accepted by professional journals, including *Nature*, *Neuroscience*, *PLoS One*, and *Molecular Psychiatry*. MIT researchers have leveraged the iPS Core Facility capabilities to receive external funding on numerous occasions.

Bioinformatics Core Facility

Bioinformatics is a branch of biological science that deals with the study of methods for storing, retrieving, and analyzing large sets of biological data. In March 2012, the Picower Institute established a bioinformatics core facility. It was constructed to use high-performance computing clusters for high-throughput quantitative data analysis. Since April 2015, the facility has provided workshops tailored to teaching the basics on use and applicability of current genomics and epigenomics software to graduate students and postdoctoral associates. Workshops highlight different themes, ranging from next-generation genomic DNA profiling, transcriptomic profiling, and transcription factor/histone code profiling to protein network analysis and visualization. The goal is for participants to learn how to use publicly available resources for bioinformatics data processing, analysis, and visualization. In 2017, the facility acquired the capability of processing high-throughput single-cell transcriptomic profiling data generated by individual Picower laboratories.

Shared Imaging Core Facility

In 2015, the Picower Institute created a shared imaging core equipment facility to allow the institute to lead brain-mapping microscopy methods. The facility includes hardware and software infrastructure for clear lipid-exchanged anatomically rigid imaging/immunostaining-compatible tissue hydrogel (CLARITY) technology. The equipment includes a high-content, rapid throughput imaging microscope system from Leica

Microsystems and Leica supporting software. The facility has been in heavy use, with the Chung, Sur, Tsai, Tye, Nedivi, Tonegawa, and Xu laboratories as the primary users. However, the equipment is available to all Picower labs and is available 24 hours a day, seven days a week. Videos and data collected using this technology are used in published research. Particularly notable are videos depicting clarified mouse and human postmortem brains, showing new pathological information for diseases such as Alzheimer's.

The Aging Brain Initiative

The Aging Brain Initiative is led by institute director Li-Huei Tsai. Senior participants include Dean Michael Sipser of MIT's School of Science and seven other founding faculty members from different disciplines. The goals of the initiative are to begin a transformative process of collaborative study, discovery, and rapid integration of brain-aging research into real-world applications, and to establish a long-term investment platform from which to address this global health imperative. The program aims to bring MIT's leading memory and neurobiology researchers together with researchers from other disciplines, including engineers, computer scientists, economists, urban planners, and social policy experts. High-risk flagship projects—created across a diverse range of expertise—include a whole-systems level perspective extending beyond the traditional clinical pathology and genetic approaches of today. Frequent multi-disciplinary discussion forums and bi-monthly seminars enable open sharing of data and accelerated pollination of ideas for growth into new areas. This year, the Aging Brain Initiative sponsored its first scientific symposium, Brain Rhythms in Health and Disease.

Other major events to raise awareness and increase the visibility of the effort this past fiscal year included an MIT Campaign Roadshow event held in Boston in September for over 1,800 MIT alumni and donors, and two breakfast events hosted by unaffiliated donor and supporter Alan Patricof at Greycroft Partners in New York City in August. The breakfast events connected the Picower Institute's efforts with several influential unaffiliated individuals from New York City, many of whom have since visited MIT to see the initiative's work firsthand. Professor Tsai was also invited to give a talk about the initiative's work to the US Congressional Biocaucus in July 2017. New gifts and pledges for the effort total $9.5 million to date and an additional $3.6 million has been documented in bequest intentions. The initiative has proposals amounting to $31.4 million under consideration.

The Aging Brain Initiative continues to focus on approaches that consist of project- and team-based research that can be implemented immediately to help us understand both healthy and unhealthy brain aging and to develop real-world solutions that reduce cognitive decline. Flagship projects currently center on the following:

- Approaches to understanding brain aging and disease informed by big data
- Circuit- and systems-level designed therapeutic approaches, including noninvasive stimulation regimens and ways to restore memory
- Personalized approaches to treatment through human and new models of disease
- Research approaches to uncovering the secrets to healthy aging and resilience

This past fiscal year, the Aging Brain Initiative expanded work on a breakthrough discovery and potential noninvasive therapy for Alzheimer's disease that was first published in December 2016. The group also expanded efforts to use a new noninvasive deep-brain stimulation technology with implications for Parkinson's disease and amyotrophic lateral sclerosis (ALS), testing prototype devices and treatment regimens in healthy human volunteers. Preliminary results are encouraging and suggest the approach is both safe and feasible in humans.

Faculty Research Summaries

Mark Bear
Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences

The overarching interest in Mark Bear's laboratory is in the question of how experience, deprivation, and disease modify synaptic connections in the brain. Experience-dependent synaptic plasticity is the physical substrate of memory. It also sculpts connections during postnatal development to determine the capabilities and limitations of brain functions, is responsible for the reorganization of the brain after damage, and is vulnerable in numerous psychiatric and neurological diseases, contributing to their symptoms.

The laboratory's major efforts to address this question have been focused on the visual cortex and hippocampus. The visual cortex is a site of robust experience-dependent synaptic plasticity, exemplified by the consequences of temporary monocular deprivation during childhood. Monocular deprivation sets in motion a stereotyped choreography of synaptic modification in which the deprived eye's inputs to visual cortex rapidly lose strength; with a delay, the open eye's inputs undergo a compensatory gain in strength. The behavioral consequence of this plasticity is severe visual impairment in the deprived eye. In humans, this condition is called amblyopia, and it is responsible for loss of vision in more than 1% of the world population. Thus, the visual cortex is an excellent preparation to connect the elementary molecular mechanisms of synaptic plasticity to their behavioral consequences. Further, insights into how synapses depress or potentiate have potential clinical applications for the treatment of amblyopia.

The hippocampus is a cortical structure that is critical to forms of learning and memory. The simple cellular architecture of the hippocampus also makes it amenable to electrophysiological investigations of synaptic plasticity that are much more difficult in other parts of the brain. In the early 1990s, researchers applied insights gained from a theoretical analysis of synaptic plasticity to establish a phenomenon called homosynaptic long-term depression (LTD). LTD is the functional inverse of long-term synaptic potentiation (LTP). Although LTD and LTP are expressed at synapses throughout the brain, they are particularly robust at the Schaffer collateral synapses in the CA1 region of the hippocampus. The hippocampus is therefore an excellent preparation in which to dissect the molecular basis of bidirectional synaptic plasticity. Insights gained here can not only be applied to synaptic modifications elsewhere in the brain, but are also relevant to understanding the basis of hippocampus-dependent memory storage and diseases of cognition.

In the course of studying LTD, Bear Laboratory members made a discovery that has turned out to have major therapeutic significance for human developmental brain disorders that cause autism. One form of hippocampal LTD is triggered by activation of metabotropic glutamate receptor 5 (mGluR5) and requires immediate translation of messenger RNAs (mRNAs) at synapses. Researchers studying this type of synaptic plasticity discovered that protein synthesis (and LTD) downstream of mGluR5 is exaggerated in the mouse model of fragile X. Human fragile X is caused by the silencing of the fragile X mental retardation 1 gene and is the most common inherited form of intellectual disability and autism. Insight gained by the study of LTD suggested that exaggerated protein synthesis downstream of mGluR5 might be pathogenic and contribute to many symptoms of the disease. Subsequent tests of the so-called mGluR theory have shown that inhibition of mGluR5 can correct multiple mutant phenotypes in animal models of fragile X, ranging from mouse to fruit fly. Human clinical trials were initiated based on the strength of this science, and results to date indicate that treatments can be developed to substantially benefit this patient population. The mGluR theory has contributed to a major paradigm shift away from the historic view that genetic diseases of brain development are untreatable to the modern view that they may be ameliorated or corrected with appropriate therapy.

Current work in the lab is focused on three related themes: mechanisms and regulation of naturally occurring synaptic plasticity in visual cortex, pathophysiology and treatment of genetically defined developmental brain disorders (particularly fragile X), and using knowledge of synaptic plasticity to promote recovery from amblyopia. Researchers primarily study mouse models, using a broad range of methods that include brain slice electrophysiology and biochemistry, in vivo electrophysiology, two-photon functional and structural imaging, and behavioral analysis. The laboratory is oriented to questions rather than to methods; laboratory members will apply any technology that is needed to address the questions of greatest interest.

Emery Brown
Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience, Institute for Medical Engineering and Science (IMES), Department of Brain and Cognitive Sciences

Recent technological and experimental advances in recording signals from neural systems have led to an unprecedented increase in the types and volume of data collected in neuroscience experiments, and in the need for appropriate techniques to analyze them. A primary focus of the research in the Brown Laboratory is the development of statistical methods and signal-processing algorithms for neuroscience data analysis, using combinations of likelihood, Bayesian, state-space, time-series, and point-process approaches. Lab members have used these methods to:

- Characterize how hippocampal neurons represent spatial information in their ensemble firing patterns
- Analyze formation of spatial receptive fields in the hippocampus during learning of novel environments

- Relate changes in hippocampal neural activity to changes in performance during procedural learning
- Improve signal extraction from functional magnetic resonance imaging (fMRI) time-series
- Characterize the spiking properties of neurons in primary motor cortex
- Localize dynamically sources of neural activity in the brain from electroencephalogram (EEG) and magnetoencephalogram recordings made during cognitive, motor, and somatosensory tasks
- Measure the period of the circadian pacemaker (human biological clock) and its sensitivity to light
- Characterize the dynamics of human heartbeats in physiological and pathological states
- Denoise two-photon in vivo imaging data

General anesthesia is a neurophysiological state in which a patient is rendered unconscious, insensitive to pain, amnestic, and immobile, while being maintained in a physiologically stable state. General anesthesia has been administered in the US for more than 160 years; currently, more than 100,000 people receive anesthesia daily in this country for surgery alone. Still, the mechanism by which an anesthetic drug induces general anesthesia remains a medical mystery. The Brown Laboratory is taking a systems neuroscience approach to study how the state of general anesthesia is induced and maintained. To do so, researchers are using fMRI, EEGs, neurophysiological recordings, microdialysis methods, and mathematical modeling in interdisciplinary collaborations with investigators in BCS, the Harvard-MIT Division of Health Science and Technology, Massachusetts General Hospital, and Boston University. The long-term goal of this research is to establish a neurophysiological definition of anesthesia; to develop safer, site-specific anesthetic drugs; and to develop better neurophysiologically based methods for measuring the depth of anesthesia.

The laboratory published two important papers this past year. One was on multimodal general anesthesia in *Anesthesia & Analgesia*; the other was on state-space multi-taper time-frequency analysis in the *Proceedings of the National Academy of Sciences*.

Kwanghun Chung
Picower Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences, IMES, Department of Chemical Engineering

Professor Kwanghun Chung is leading an interdisciplinary research team devoted to developing and applying novel technologies for holistic understanding of large-scale complex biological systems. Specifically, the team developed a number of methods, including the brain imaging technique known as CLARITY, the system-wide control of interaction time and kinetics of chemicals (SWITCH), stochastic electrotransport, and a magnified analysis of proteome (MAP) technique that may enable identification of multiscale functional networks and interrogation of their system-wide, multifactorial

interactions. Lab members are applying these technologies to studying brain function and dysfunction using animal models, human clinical samples, and organoid systems.

In the past year, the Chung group continued to develop new technologies to accelerate the pace of scientific discovery and development of therapeutic strategies in a broad range of biomedical research. Recent research advances include the development of SHIELD technology, which simultaneously and globally protects tissue physicochemical properties while allowing multiscale molecular imaging. The Chung Lab has shared the SHIELD reagents and protocols with more than 40 labs worldwide. The group has active collaborations with researchers at MIT, at the Broad Institute, at Massachusetts General Hospital, and Harvard University; members of the group have co-authored eight articles in the past year. Professor Chung has traveled extensively, including to the University of Munich, Merck, Columbia University, Seoul National University, and the University of British Columbia, as well as to Gordon research conferences to speak about his group's technologies and their applications. Chung taught 10.302 Transport Processes and HST.562 Pioneering Technologies in Biology and Medicine. He has recently founded a start-up firm, LifeCanvas Technologies, which aims to advance the adoption and use of Chung Lab technologies developed at MIT.

Steven Flavell
Lister Brothers Career Development Assistant Professor,
Department of Brain and Cognitive Sciences

Action potentials and synaptic transmission occur over the time scale of milliseconds, yet the brain generates behaviors that can last seconds, minutes, or hours. A major goal of neuroscience is to understand how neural circuits generate coherent behavioral outputs across such a wide range of time scales. Sustained behavioral states—including arousal states (sleep, wake) and complex internal states (emotions)—are thought to be controlled by biogenic amine and neuropeptide neuromodulators. However, we still have a poor understanding of the basic neural mechanisms that underlie behavioral state initiation, maintenance, and termination. Moreover, it is unclear how external and internal cues, such as satiety status, alter the outputs of the neural circuits that control these states. The goal of the Flavell Lab is to understand how neural circuits generate sustained behavioral states and how physiological and environmental information is integrated into these circuits.

Professor Flavell's recent studies have identified a neuromodulatory circuit that generates two opposing behavioral states in *C. elegans*. Using quantitative behavioral analyses paired with genetics, Flavell showed that serotonin and the neuropeptide PDF each act to initiate and extend one behavioral state while inhibiting the other state, resulting in a flip-flop switch that determines state stability. He performed in vivo calcium imaging (GCaMP) and optogenetics (channelrhodopsin) to examine the temporal relationship between neuromodulation and behavioral transitions. He also identified the exact neurons within the *C. elegans* connectome that make up this neuromodulatory circuit. This work demonstrated how neuromodulation supplements fast motor circuits with slow temporal dynamics, organizing behaviors into long-lasting states.

Professor Flavell is now asking fundamental questions about how behavioral states are generated and how environmental cues influence state generation. For example, what circuit-wide patterns of activity define the stable configurations for each behavioral state? How are these patterns stabilized by neuromodulators such as serotonin? Toward this end, the Flavell Laboratory has constructed a microscope that is suitable for whole-brain calcium imaging and is using this new technology to characterize large-scale neural activity patterns associated with distinct behavioral states.

Other fundamental questions include:

- How do neural circuits detect the feeding or satiety status of an animal so that only certain behavioral states are generated while food is available? The Flavell Lab identified a conserved family of ion channels that may mediate satiety sensing by neurons and is completing their characterization of these new channels.
- How do animals compare current food levels with those of the recent past and adjust behavior accordingly? Researchers have taken advantage of new cell-specific molecular profiling methods to examine how gene expression changes in animals with different feeding experiences. They found that the chemoreceptors for smell and taste show striking expression changes in response to changes in nutritional state.
- Researchers have also expanded their studies to examine more broadly how animals coordinate and structure their behavior. They built a set of microscopes that can record *C. elegans* over their entire lifespans and developed machine vision software to automatically quantify every behavior generated by an animal. This technology will soon be coupled to the whole-brain calcium imaging approach outlined earlier. By linking large-scale neural activity to a comprehensive understanding of behavioral structure, this work should provide fundamentally new insights, revealing how the brain generates a structured and coordinated set of behavioral outputs.

Myriam Heiman
Latham Family Career Development Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences, Core Member, Broad Institute

The most common neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's disease, display distinct clinical presentations. The basis of these distinct clinical presentations is the enhanced vulnerability of certain neuronal types to death or dysfunction. Work in the Heiman Lab is broadly interested in this phenomenology of enhanced vulnerability in neurodegenerative disease; researchers view it as an opportunity to discover valuable insights into the cell biology of each disease-relevant neuronal cell type, as well as to identify new therapeutic targets. Laboratory members are using innovative approaches to address these long-standing questions of selective vulnerability, which have remained open questions in the field for decades.

In the past year, the lab's cell-type-specific molecular profiling studies in Huntington's disease models have revealed early homeostatic changes in response to mutant Huntingtin, including the observation that there are early changes to the transcription

factor Foxp2 and retinoic acid-dependent signaling in vulnerable neurons. The identification of early changes induced by mutant Huntingtin offered several new therapeutic targets for further testing. In a separate line of research, using a genome-wide, unbiased in vivo genetic screening methodology, researchers identified a number of modifiers of mutant Huntingtin neuronal toxicity in pathways previously implicated in Huntington's disease and in several novel targets. One of these, a gene linked to maintenance of proper protein folding, has been validated in vivo and will be further pursued as a therapeutic target.

In addition to these Huntington's disease-relevant studies, researchers finished performing extensive molecular profiling of neuronal subtypes under chronic administration of both typical and atypical antipsychotic drugs that are used to treat schizophrenia. These studies uncovered a core molecular signature of genes whose expression is altered in neurons upon chronic treatment with any typical or atypical antipsychotic drug. Laboratory members have observed and functionally validated that the drug clozapine, considered to be the superior atypical antipsychotic drug, induces transcriptional alterations only in certain subtypes of schizophrenia-relevant neurons, unlike all other antipsychotic drugs. The hope is that these findings can be used for future rational antipsychotic drug design. In various collaborations, members of the Heiman Lab have applied a cell-type-specific methodology (translating ribosome affinity purification methodology) and were involved in helping to demonstrate that normal brain aging induces A1-like astrocyte reactivity, as well as the accumulation of cleaved untranslated fragments of mRNAs.

Troy Littleton
Menicon Picower Professor of Neuroscience,
Departments of Biology and Brain and Cognitive Sciences

Research in the Littleton Lab is aimed at characterizing the mechanisms by which neurons form synaptic connections, how synapses transmit information, and how synapses change during learning and memory. Laboratory members combine molecular biology, protein biochemistry, electrophysiology, and neuroimaging approaches with *Drosophila* genetics to address these questions. A major effort has been to characterize the molecular machinery that mediates synaptic vesicle fusion, focusing on how the calcium sensor synaptotagmin and the fusion clamp complexin interface with the SNARE complex to control neurotransmitter release. The lab has also developed transgenic tools to spatially visualize synaptic vesicle fusion events at single active zones, defining general rules for how individual release sites function and identifying a new category of "spontaneous only" active zones that revealed novel roles for minis in synaptic development and function. In addition, Professor Littleton has used the *Drosophila* model for the study of several neurological disorders, including epilepsy, Huntington's disease, and autism.

Earl Miller
Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences

The overarching goal of Earl K. Miller's laboratory is to understand cognitive functions in a broader context as a product of interactions between networks and circuits of neurons, brain areas, and systems. To this end, the Miller Laboratory has developed (and shares) technology and techniques for recording from many separately movable, acutely inserted electrodes. These recordings allow the gap between the global scope of human brain imaging and the spatiotemporal precision of single-neuron physiology to be bridged. It also allows examination of precise timing relationships and interactions between neuronal populations. The laboratory couples this with investigating the kind of sophisticated, flexible behaviors at which humans and nonhuman primates are so adept.

In the past year, researchers in the Miller Lab made discoveries that suggest that rhythmic synchrony between neurons (brain waves) plays an important role in consciousness and learning. They found that when animals learn new categories, brain wave synchrony between cortical areas increases. They also found that loss of consciousness may occur when anesthesia hyper-synchronizes neurons to slow brain waves, preventing normal communication. These findings suggest that brain waves play a major role in regulating neural communication.

Elly Nedivi
Picower Professor, Departments of Brain and Cognitive Sciences and Biology

The Nedivi Laboratory studies the cellular mechanisms that underlie activity-dependent plasticity in the developing and adult brain through studies of neuronal structural dynamics, identification of the participating genes, and characterization of the proteins they encode. After identifying a large number of candidate plasticity genes (CPGs), researchers elucidated the neuronal and synaptic function of two previously unknown CPGs, CPG15 and CPG2, and showed that each provides unique insight into diverse aspects of plasticity mechanisms. Both molecules have subsequently become well known; CPG15 (later named neuritin) is an extracellular ligand with multiple roles inside and outside the nervous system, and CPG2 is a product of SYNE-1, one of the best genetic markers for bipolar disorder. Motivated by the large number of CPGs that affect neuronal structure, the Nedivi Lab has a long-standing collaboration with Peter So's lab in the Department of Mechanical Engineering to develop multi-photon microscopy for large-volume, high-resolution imaging of dendritic arbor and synaptic structural dynamics in vivo. Recently, we have developed methods for labeling and chronic monitoring of excitatory and inhibitory synapses across entire neuronal arbors in the mouse visual cortex in vivo.

Mriganka Sur
Paul E. Newton Professor of Neuroscience, Department of Brain and Cognitive Sciences, Director, Simons Center for the Social Brain

Members of Mriganka Sur's laboratory study the development, plasticity, and dynamics of the cerebral cortex. Insights from studies of brain development can be used to understand mechanisms of developmental brain disorders. The laboratory's discoveries in academic year 2018 included three major findings.

Locally coordinated synaptic plasticity of visual cortex neurons in vivo
Neuronal circuits in the brain are subject to changes driven by sensory inputs or motor learning, causing cells to modify their responses to individual inputs while maintaining a stable level of activity. Synaptic potentiation at specific dendritic locations could be coordinated with heterosynaptic depression of nearby synapses within short stretches of the same dendrite to co-operatively implement functional plasticity of single-cell responses. The manner in which different forms of synaptic plasticity act together to create functional changes in neurons remains unknown. By imaging responses of single synapses in identified neurons of mouse visual cortex in vivo, combined with targeted strengthening of specific synapses, researchers found that spike-timing-induced receptive field plasticity of visual cortex neurons is anchored by increases in synaptic strength of identified spines. This is accompanied by a decrease in the strength of adjacent spines on a slower time scale. The locally coordinated potentiation and depression of spines involves prominent AMPA receptor redistribution via targeted expression of the immediate early gene Arc. Similar changes in strengthened synapses, combined with weakening of adjacent synapses, accompany recovery of eye-specific drive in identified neurons following monocular deprivation. Hebbian strengthening of activated synapses and heterosynaptic weakening of adjacent synapses thus co-operatively orchestrate cell-wide plasticity of functional neuronal responses.

Task-dependent representations of stimulus and choice in mouse parietal cortex
Perceptual decision making involves multiple cognitive processes, including processing sensory stimuli, accumulating evidence, and transforming sensory information into an appropriate motor plan. Although many brain regions have been implicated in perceptual decisions, dissociating their individual contribution to these different processes remains a challenge. The posterior parietal cortex has been implicated in perceptual decisions, but whether its role is specific to sensory processing or sensorimotor transformation is not well understood. Researchers trained mice to perform a go/no-go visual discrimination task and imaged the activity of neurons in primary visual cortex (V1) and PPC during engaged behavior and passive viewing. Unlike V1 neurons, which responded robustly to stimuli in both conditions, most PPC neurons responded exclusively during task engagement. To test whether signals in the PPC primarily encoded the stimulus or the animal's impending choice, we imaged the same neurons before and after re-training mice with a reversed sensorimotor contingency. Unlike V1 neurons, most PPC neurons reflected the animal's choice of the new target stimulus after retraining. Mouse PPC is therefore strongly task-dependent, reflects choice more than stimulus, and may play a role in the transformation of visual inputs into motor commands.

Major vault protein, a candidate gene in 16p11.2 microdeletion syndrome, is required for the homeostatic regulation of visual cortical plasticity
Microdeletion of a region in chromosome 16p11.2 increases susceptibility to autism and accounts for up to 1% of the population with autism spectrum disorder. Although this region contains exons of 29 genes, disrupting only a small segment of the region that spans five genes is sufficient to cause autistic traits. One candidate gene in this critical segment is *MVP*, which encodes for the major vault protein (MVP) that has been implicated in regulation of cellular transport mechanisms. MVP expression levels in

MVP$^{+/-}$ mice closely phenocopy those of 16p11.2 mutant mice, suggesting that *MVP*$^{+/-}$ mice may serve as a model of MVP function in 16p11.2 microdeletion. This study showed that MVP regulates the homeostatic component of ocular dominance plasticity in primary visual cortex (V1). *MVP*$^{+/-}$ mice show impairment in strengthening of open-eye responses after several days of monocular deprivation, while closed-eye responses are weakened as is normal, resulting in reduced overall ocular dominance plasticity. The frequency of miniature excitatory postsynaptic currents (mEPSCs) in pyramidal neurons is decreased in *MVP*$^{+/-}$ mice after extended monocular deprivation, suggesting a decrease in the number of functional synapses. Correspondingly, upregulation of surface GluA1 AMPA receptors is reduced in *MVP*$^{+/-}$ mice after extended monocular deprivation and is accompanied by altered expression of STAT1 and phosphorylated ERK, which have been previously implicated in ocular dominance plasticity. Normalization of STAT1 levels by introducing STAT1 short hairpin RNA rescues surface GluA1 and open eye responses, implicating STAT1 as a downstream effector of MVP. These findings demonstrate a specific role for MVP as a key molecule influencing the homeostatic component of activity-dependent synaptic plasticity, and potentially the corresponding phenotypes of 16p11.2 microdeletion syndrome.

Susumu Tonegawa
Picower Professor of Neuroscience,
Departments of Biology and Brain and Cognitive Sciences

The primary research interest in the Tonegawa Laboratory continues to be the molecular, cellular, and systems neuroscience of learning and memory. At the heart of memory research is whether one can identify a population of neurons and their circuit that holds a specific memory. Although some earlier studies implicated a restricted brain area or region in holding a particular type of memory (e.g., the hippocampus for explicit memory, the IT complex for visual memory, and the cerebellum for motor memory), none of these studies causally identified a specific neuronal population as the holder of a specific memory. Researchers have been particularly interested in deciphering cellular and neural circuit mechanisms underlying the encoding, consolidation, and retrieval of episodic memory—memories of events that one experiences on a daily basis. Episodic memory is the association of objects, space, and time, for which the hippocampus and entorhinal cortex play a crucial role, although other subcortical and cortical areas also participate. It has long been thought that memory is stored as lasting physical and chemical changes in the brain network (as so-called engrams). For a population of neurons to qualify as engram cells, at least three conditions must be met. First, these neurons are activated by learning; second, lasting physical and chemical changes are induced in them; and third, their subsequent reactivation by recall cues induces behavioral recall.

Researchers in the Tonegawa Lab published a milestone paper showing the sufficiency and necessity of an engram for a specific memory. Lab members continue to elucidate engram mechanisms for various types of memory (e.g., emotional or social memory), including consolidation and retrieval. They are also evaluating applications of such knowledge that could facilitate the amelioration of human brain disorders such as Alzheimer's disease. Currently, researchers are focused specifically on several important questions that are critical for a better understanding of memory in the mammalian brain:

- Identifying the role of engram excitability in memory retrieval
- Characterizing the role and mechanism of prefrontal cortex engrams in memory consolidation
- Determining the role of hippocampal vCA1 neurons in social disorders such as Alzheimer's disease
- Elucidating the role of the basolateral amygdala in fear extinction

Li-Huei Tsai
Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences

Members of the Tsai Laboratory are interested in elucidating the pathogenic mechanisms underlying neurological disorders that impact learning and memory. They are taking a multidisciplinary approach to investigating the molecular, cellular, and circuit basis of neurodegenerative disorders.

Recent advances include the following:

Identification of novel disease-stage immune cell populations critical for modulating immune response during neurodegeneration

Microglia, the primary resident macrophages of the brain, are responsible for immune surveillance within the brain against environmental disturbance and threats such as microbial pathogens. However, how microglia respond to neuronal death during the course of neurodegeneration is not clear. Researchers used a single-cell transcriptional approach to profile gene expression of individual microglia from the hippocampus of a mouse model for Alzheimer's disease with rapid and severe neurodegeneration. This approach allowed us to identify previously unobserved heterogeneity in the response of microglia to neurodegeneration. Distinct subpopulations of microglia were found to be reprogramming their gene expression profiles to respond to specific states of the disease. This discovery paves the way for a better understanding of the dynamic response and contributions of novel brain cell subpopulations to disease progression during neurodegeneration.

Discovery of how ApoE4 impacts specific brain cell types in Alzheimer's disease
Individuals carrying the ApoE4 allele have a high risk for developing late-onset Alzheimer's disease. Despite considerable research, it remains unclear how this allele differs from the more common and benign ApoE3 allele in conferring higher risk for Alzheimer's disease. Researchers created induced pluripotent stem cell (iPSC) lines that were genetically identical except for the ApoE allele and differentiated them into different brain cell types to determine how ApoE4 affects the function of neurons and other brain cell types. They found that compared with ApoE3, ApoE4 affects the functions of multiple brain cell types in a manner that promotes the development of Alzheimer's pathology. In neurons, they increased beta amyloid and aberrant early endosomes; lipid metabolism was defective in astrocytes and microglia showed compromised phagocytic functions and dysregulated expression of immune genes. The critical role of ApoE4 in Alzheimer's disease pathogenesis was further highlighted by the fact that when researchers used genome editing to change ApoE4 in iPSCs derived from

patients with late-onset Alzheimer's disease to ApoE3, most of the Alzheimer's disease–related pathologies seen with the ApoE4 cell types was attenuated. The study opens up potential new avenues for therapeutic intervention by coaxing ApoE4 to behave more like ApoE3 in relevant Alzheimer's disease–associated cell types.

Kay Tye
Picower Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences

Since Kay Tye's arrival at the Picower Institute in January 2012, she has been working to use cutting-edge neuroscience approaches to identify the circuit and synaptic mechanisms underlying emotional processing and motivated behaviors in both health and disease in rodent models. The long-term objective of the laboratory's work is to identify common circuit perturbations that may underlie comorbidity between psychiatric disease states such as addiction, anxiety, and depression. To do this, the Tye Lab employs an interdisciplinary approach integrating electrophysiological, optogenetic, pharmacological, and imaging techniques to study the neural bases of behavior.

Members of the Tye Lab investigated the influence of an acute, severe stressor on the mesolimbic dopamine system within the ventral tegmental area in the female brain and showed long-lasting neural as well as behavioral changes. They followed up on previous work with an in-depth analysis of the intricate interaction of different projection populations of the basolateral amygdala and the influence of homeostatic needs on these interactions. Researchers overlaid anatomical projection target locations of the basolateral amygdala in a three-dimensional map with its encoding properties during cue discrimination, improving our understanding of the functional as well as topographical organization of this circuit underlying valence assignments. Researchers then showed that the neurons projecting from the anterior cingulate cortex to the basolateral amygdala play a pivotal role in observational fear learning. It is a considerable challenge to identify ensembles of neurons that participate in complex behaviors that may be intermingled with neurons of distinct functions.

Tye Lab members developed a temporally precise activity-dependent tool that allows the expression of any transgene (opsins, fluorescent proteins, calcium indicators, and so on) when neurons that have elevated calcium levels are illuminated. Additionally, researchers collaborated with Ian Wickersham in the development of novel, nontoxic rabies viral vectors for retrograde targeting of neurons. Working together, Tye laboratory researchers hope to connect the mesolimbic dopamine system with the amygdalar glutamatergic network and to identify common pathways that may underlie multiple behavioral phenotypes relevant to anxiety, addiction, and depression.

Matthew Wilson
Sherman Fairchild Professor in Neurobiology,
Departments of Brain and Cognitive Sciences and Biology

Work in Matthew A. Wilson's laboratory continues to focus on the role of the hippocampus in the formation, maintenance, and use of memory in the mammalian nervous system during awake and sleep states. Previous experiments have shown that

the hippocampus reactivates memories of recent experience during sleep in what may be described as the animal correlate of dreaming. They have also demonstrated that reactivation of specific memories can be triggered through the use of auditory cues, effectively "engineering" dream content and providing the means to establish a causal relationship between memory processing during sleep and subsequent awake behavior. They have also shown that hippocampal memory reactivation that occurs while animals stop briefly on a maze to "think" is paired with information about anticipated rewards, providing insights into potential mechanisms of goal-directed planning and decision making. Using optogenetic approaches to manipulate neural activity, lab members identified novel circuits involved in the regulation of attention and sleep, and demonstrated the role of brain rhythms in enhancing memory performance.

Weifeng Xu
Picower Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences

The Xu Laboratory studies how experience shapes excitatory circuit connectivity. Researchers use a combination of molecular, cellular, biological, electrophysiological, and behavioral analyses in the rodent model system to study critical players in experience-dependent excitatory synapse patterning during development and learning and memory. The mechanisms are associated with major mental disorders including autism, schizophrenia, bipolar disorder, and intellectual disability. Understanding the underlying mechanisms for experience-dependent synapse patterning will help us understand the fundamental mechanisms of information processing and storage in the brain and identify therapeutic targets for major mental disorders. The specific research direction focuses on how signaling events are coordinated by scaffold proteins and regulation of calcium homeostasis to achieve signaling specificity.

Li-Huei Tsai
Director, Picower Institute for Learning and Memory
Picower Professor of Neuroscience