Picower Institute for Learning and Memory

The Picower Institute for Learning and Memory (PILM) 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, to 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

Professor Emery N. Brown: John and Elizabeth Phillips Award, Phillips Exeter Academy; elected member of the board of directors, Simons Foundation

Assistant Professor Gloria Choi: Nancy Lurie Marks Family Foundation Career Development Award; Walter B. Brewer Fund for Science Innovation

Professor Kwanghun Chung: Presidential Early Career Award for Scientists and Engineers

Assistant Professor Steven Flavell: McKnight Scholars Award

Professor Myriam Heiman: Department of Brain and Cognitive Sciences (BCS) Award for Excellence in Undergraduate Teaching

Professor Troy Littleton: BCS Award for Excellence in Undergraduate Advising

Professor Earl Miller: doctor of science (Honoris Causa), Kent State University

Professor Elly Nedivi: elected member of the Dana Alliance for Brain Initiatives

Professor Li-Huei Tsai: elected fellow of the National Academy of Inventors

Gwyneth Margaret Welch (Tsai Lab graduate student): Ruth L. Kirschstein National Research Service Award individual predoctoral fellowship

Sandya Subramanian (Brown Lab graduate student): 2020–2021 Collamore-Rogers Fellowship

Cassi Estrem (Flavell Lab postdoctoral researcher): Ruth L. Kirschstein Postdoctoral Individual National Research Service Award

Héctor de Jesús-Cortés (Bear Lab postdoc): El Mundo Boston Latino 30 under 30 Award

Andres Crane (Littleton Lab graduate student): Angus MacDonald Award for Excellence in Undergraduate Teaching

Karen Guadalupe Cruz (Sur Lab graduate student): Angus MacDonald Award for Excellence in Undergraduate Teaching

Vaibhavi Shah (Sur Lab UROP): 2020–2021 Barry Goldwater Scholarship

Grayson Sipe (Sur Lab postdoc): 2020 Infinite Kilometer Award, School of Science

Taylor Johns (Sur Lab laboratory manager): 2020 Infinite Mile Award, School of Science

Eleanor Ricci-MacPhail (Sur Lab, Simons Center for the Social Brain administrative manager): 2020 MIT Excellence Award

Research Advances

Below, Picower Institute faculty laboratories summarize major research advances made during the report period.

Mark Bear's lab made the breakthrough discovery that therapeutic action of lithium in fragile X syndrome is mediated by inhibition of a single isoform of glycogen synthase kinase, which can be targeted to develop novel medicines for this disorder.

Kwanghun Chung's lab developed ELAST technology that transforms human brain tissues into elastic hydrogels to enhance macromolecular accessibility and mechanical stability simultaneously (published in *Nature Methods* in 2020).

Steven Flavell's lab invented a new, open-source microscopy platform that allowed them to reveal a key new insight. Dopamine signaling allows neural circuits to generate coordinated behaviors. Behavioral states, for example different arousal states, exert a widespread influence on brain function, spanning multiple sensory modalities and motor systems. The lab recently investigated this phenomenon at whole-organism scale in C. elegans. For the first time ever in any animal, they simultaneously quantified each motor program over hours or days, yielding comprehensive records of each C. elegans individual's behavior (Nathan Cermak, Stephanie K. Yu, Rebekah Clark, Yung-Chi Huang, Saba N Baskoylu, and Steven W. Flavell, "Whole-Organism Behavioral Profiling Reveals A Role for Dopamine in State-Dependent Motor Program Coupling in *C. Elegans*," *eLife* 9). These recordings revealed widespread coordination among motor programs as animals switched states. They then identified a dopaminergic circuit that mediates state-dependent coupling of the motor programs. This line of research is yielding new insights into how animals coordinate their behaviors as they transition between states, and has opened up a new model system for understanding the function of dopaminergic circuits.

Myriam Heiman's lab accomplished several research advances:

- Conducted the first in vivo, genome-wide genetic screen to identify genes that modulate neuronal survival in a normal and Huntington's disease context
- Showed that the gene Nme1 modulates Huntington's disease model symptoms
- Showed that deficiency of the cytokine interleukin 6 exacerbates Huntington's disease model symptoms
- Showed that chronic treatment with the antipsychotic clozapine prevents compulsive cocaine self-administration in mice
- Helped to identify axon plasticity genes linking A-beta, aging, and tau in Alzheimer's disease-vulnerable neurons
- Helped to characterize a cortical-brainstem circuit that predicts and governs compulsive alcohol drinking
- Helped to characterize a small molecule that shows promise in clearing misfolded proteins by rerouting them toward lysosomal degradation

Troy Littleton's lab explored how both invertebrate and vertebrate nervous systems display synaptic plasticity in response to behavioral experiences, indicating underlying mechanisms that emerged early in evolution. Recently they established a system to differentially manipulate two distinct types of drosophila motoneurons (tonic versus phasic) that display distinct forms of plasticity and presynaptic output. The team discovered that tonic motoneurons show robust types of both structural and functional plasticity compared to phasic motoneurons, allowing them to define underlying molecular mechanisms that generate neuronal synaptic diversity.

Earl Miller's lab made two noteworthy research breakthroughs: predictive routing and achieving stable dynamics in neural circuits.

The lab found evidence for a new model of a fundamental cortical function: predictive coding. Lest it be overwhelmed, the cortex filters out most sensory inputs. According to predictive coding, predictions inhibit the feeding forward of expected inputs. Unexpected violations, being informative, are fed forward. It has been unclear how the brain implements this. The predictive routing model posits that predictions feedback is implemented via alpha/beta (~8-30 Hz) rhythms in deep cortical layers. They inhibit the superficial layer activity (spiking and gamma, >35 Hz) that feed forward sensory inputs. This has direct implications for understanding and treatment of brain disorders. Regulating sensory input is the most basic cortical function. It is thought to go awry in autism (where every input is a violation) and psychosis (where predictions may overwhelm reality).

The brain consists of many interconnected networks with time-varying, partially autonomous activity. There are multiple sources of noise and variation yet activity must converge to a stable, reproducible state (or sequence of states) for computations to make sense. Taking a control-theory perspective by applying contraction analysis to recurrent neural networks the lab revealed mechanisms for achieving stability in multiple connected networks with biologically realistic dynamics, including synaptic plasticity and time-varying inputs. These mechanisms included inhibitory Hebbian plasticity, excitatory anti-Hebbian plasticity, synaptic sparsity, and excitatory-inhibitory balance. The findings shed light on how stable computations might be achieved despite biological complexity. Crucially, the analysis is not limited to analyzing the stability of fixed geometric objects in state space (e.g., points, lines, and planes), but rather the stability of state trajectories that may be complex and time-varying.

Elly Nedivi's lab advanced in vivo microscopy. Today's gold standard for imaging through scattering tissue in live animals is the point-scanning, two-photon microscope (PSTPM). However, due to sequential scanning, PSTPM is slow. Temporal focusing microscopy (TFM) works much faster by focusing femtosecond pulsed laser light temporally, while keeping wide-field illumination. However, due to the use of a camera detector, TFM suffers from the scattering of emission photons, producing images of poor spatial resolution and signal-to-noise ratio (SNR) that obscure fluorescent signals from small structures, such as dendritic spines. The team recently developed a data-driven, deep learning approach to improve TFM image resolution and SNR. Using a 3D convolutional neural network (CNN) they built a map from TFM to PSTPM modalities to enable fast TFM in vivo imaging with high resolution and SNR. They demonstrated

this approach by imaging dendritic spines on pyramidal neurons in the mouse visual cortex, and showed that the trained network rapidly outputs images that recover biologically relevant features previously buried in scattered TFM images. In vivo imaging combining TFM and the CNN is one to two orders of magnitude faster than PSTPM but retains the resolution and SNR to analyze small fluorescent structures. The CNN could also help improve the performance of many speed-demanding, deep-tissue imaging applications such as in vivo voltage imaging.

Mriganka Sur's lab achieved several breakthroughs: distinct prefrontal top-down circuits differentially modulate sensorimotor behavior; pharmacological enhancement of KCC2 gene expression exerts therapeutic effects on human Rett syndrome neurons and MECP2 mutant mice; noradrenergic signaling in the wakeful state inhibits microglial surveillance and ynaptic plasticity in the mouse visual cortex; and motor cortex astrocytes contribute to motor learning and neuronal coding in vivo.

Sensorimotor behaviors require prioritizing processing of behaviorally relevant sensory cues and selecting appropriate responses. Top-down modulation by the prefrontal cortex (PFC) is key for both processes, but the precise function of specific PFC circuits remains unclear. We examined two outputs in sensorimotor control from within a mouse PFC subdivision, the anterior cingulate cortex (ACC), using diverse circuit dissection techniques and multiple task contingencies. Targeted two-photon calcium imaging and optogenetic manipulations show that ACC outputs to the superior colliculus principally coordinate specific motor responses. ACC outputs to the visual cortex facilitate visual cue processing. These results demonstrate that anatomically nonoverlapping PFC outputs modulate sensorimotor processing by complementary mechanisms, and suggest an organizing principle for top-down modulation of sensorimotor behaviors.

Rett syndrome (RTT) is a neurodevelopmental disorder caused by mutations in the methyl CpG binding protein 2 (MECP2) gene. There are no approved treatments. Expression of K^+/Cl^- cotransporter 2 (KCC2), a neuron-specific protein, is reduced in human RTT neurons and in RTT mice, suggesting that KCC2 might contribute to RTT pathophysiology. We developed a neuron-based, high-throughput screening assay to identify compounds that enhance KCC2 expression in genome-edited human reporter neurons. From an unbiased screen of more than 900 small-molecule chemicals, we identified a group that enhance KCC2 expression, termed KCC2 expression–enhancing compounds (KEECs). The KEECs include US Food and Drug Administration-approved drugs that inhibit the fms-like tyrosine kinase 3 or glycogen synthase kinase 3β pathways and activators of the sirtuin 1 and transient receptor potential cation channel subfamily V member 1 pathways. KEEC treatments increased KCC2 expression in human wild-type and isogenic MECP2 mutant RTT neurons, and rescued electrophysiological and morphological abnormalities of RTT neurons. Injection of KEEC KW-2449 or piperine in MECP2 mutant mice ameliorated disease-associated respiratory and locomotion. The compounds may have therapeutic effects not only in RTT but also in other neurological disorders involving KCC2 dysregulation.

Microglia are the brain's innate immune cells and have a role in synaptic plasticity. Microglial processes continuously survey the brain parenchyma, interact with synaptic elements and maintain tissue homeostasis. However, the mechanisms that control

surveillance and its role in synaptic plasticity are poorly understood. Microglial dynamics in vivo have been primarily studied in anesthetized animals. Studies done by the Sur Lab and fellow collaborators in the University of Rochester Medical Center showed that microglial surveillance and injury response are reduced in awake mice compared to anesthetized mice, suggesting that arousal state modulates microglial function. Pharmacologic stimulation of β2-adrenergic receptors recapitulated these observations and disrupted experience-dependent plasticity. These effects required the presence of β2-adrenergic receptors in microglia. These results indicate that microglial roles in surveillance and synaptic plasticity in the mouse brain are modulated by noradrenergic tone mediated by arousal states, and emphasize the need to understand the effect of disruptions of adrenergic signaling in neurodevelopment and neuropathology.

Motor cortex, including M1, is crucial for the production of precise and reliable movements, yet its functions and plasticity during motor learning are not fully understood. The contribution of M1 astrocytes and the physiological role of M1 astrocyte-neuron interactions during motor learning is unknown. Sur Lab researchers reported that astrocyte-specific manipulation of M1 in mice, targeting glutamate clearance and Gq signaling, regulate motor learning and performance by modulating neuronal activity and encoding. Mice expressing decreased levels of the astrocyte glutamate transporter GLT1 in M1 showed normal success rate but impaired learning of a stereotyped movement; M1 neuronal populations were more active but encoded less task information. Mice with increased astrocyte Gq signal activation in M1 showed decreased success rate and decreased learning of the stereotyped movement; these features accompanied high levels of neuronal signal correlation, low encoding of movement parameters, and altered encoding of correct trials. Analysis of gene expression from purified M1 astrocytes during the task suggested gene expression modulation associated with motor learning. This included regulation of genes involved in glutamate transport and GPCR signaling, which may underlie the influence of astrocytes on neuronal circuits and population encoding that we demonstrate.

Susumu Tonegawa's lab achieved the impressive discovery of an independent hippocampal code: a so-called event code, dedicated to organizing experience by events as discrete and transferable units. This study was published in *Nature Neuroscience* and has received widespread response.

In Li-Huei Tsai's lab recent advances include the following:

Identifying a role for the histone deacetylase HDAC1 in the repair of oxidative DNA damage in brain aging and Alzheimer's disease. HDAC1 stimulates the enzyme OGG1 to remove 8-oxoG, a major species of oxidative DNA damage, at promoters of genes important in brain functions. Activating HDAC1 with small molecule could reduce 8-oxoG lesions in normal aging mice and mouse model of Alzheimer's disease. The lab recently published these results in *Nature Communications*.

The lab also developed an in vitro human blood-brain barrier (BBB) using induced pluripotent stem cells derived from individuals carrying APOE4, a strong genetic risk factors for developing cerebral amyloid angiopathy (CAA) and Alzheimer's disease. They showed both in vitro and in vivo that APOE4 expression in pericytes, the smooth

muscle cells of the BBB, resulted in dysregulated calcineurin-NFAT signaling and CAA-associated pathology. By blocking the calcineurin-NFAT pathway with FDA-approved drugs, they ameliorated CAA pathology associated with APOE4 in a mouse model of Alzheimer's disease. The lab published these results in *Nature Medicine*.

Personnel

More than 282 community members participated in Picower Institute activities during the report period, the numbers breakdown as follows: 13 faculty members; three visiting scientists/scholars; 56 postdocs; 26 research scientists; 38 undergraduates; 33 graduate students; 60 research and technical staff; 18 administrative and service staff; and 35 research affiliates.

Items of note during the academic year include the following:

- Maria del Carmen Levy joined as financial coordinator in August 2020, replacing Silvia Darosa.
- Picower Institute added a new financial administrator position and the search is ongoing.
- Athene Wilson-Glover joined as administrative assistant to Mark Bear in January 2020, replacing Jessica Buckey.
- Thomas Garvey joined as senior administrative assistant to Li-Huei Tsai in January 2020, replacing Kathleen Fitzgerald.
- Darnell Reese joined as development assistant to Asha Bhakar in November 2019, replacing Tania Kyle.
- In July, Kwanghun Chung transferred more than half of his funding and lab members to PILM from IMES.

Resource Development

The Picower Institute's impressive success over recent years continued in FY2020. These attainments reflect the faith of PILM's most generous alumni and friends, along with numerous corporations and foundations, in Picower Institute's ability to make valuable use of private resources. Picower resource development (RD) efforts identified and publicized more than 129 formal foundation and government funding requests, extended Neuroscience News' (the Picower Institute's print newsletter) outreach to 2,661 individuals worldwide, hosted more than 108 personalized and virtual visits with prospective and current donors, and helped host two major online development events to extend our visibility and relationships with a larger audience. With support from Picower Institute's communications director, RD worked with Picower faculty to draft 12 prize nominations and 34 new formal philanthropic proposals. Outright gift payments to PILM for FY2020 totaled more than $17.7 million and new philanthropic gifts and pledges totaled more than $10.6 million.

With the generous support provided from the JPB Foundation, Barbara Picower and the late Jeffry Picower, researchers at the Picower Institute have continued their ambitious research efforts. A new JPB gift commitment, totaling $4.92 million renewed and expanded the Picower Fellows program, an opportunity to recruit and retain top-level postdocs and clinical scientists to PILM. This program has supported 45 exceptional individuals, including 31 international scholars, 17 women scientists, and two PILM members from underrepresented minority groups. A new, second gift of $300,000 will support emergency Tsai Lab research to understand how Sars-CoV-2 infects and causes pathology in the vasculature and brain. In FY2020, a total of $7.19 million in outright gift payments from the JPB Foundation continued to support all major Picower Institute research programs and a few individual lab awards. These include the Picower Institute Innovation Fund (PIIF), the Picower Fellows program, the Catalyst Program, Junior Faculty Awards, and support for Susumu Tonegawa's laboratory.

The PIIF is the Picower Institute's flagship program created to empower PILM scientists to take risks as they conduct research into the greatest challenges and fundamental mysteries of neuroscience. To date, the PIIF has leveraged more than $70 million in additional grant funding to the Picower Institute, generated more than 232 publications, launched three companies, and has been the basis for global collaboration, firmly establishing PILM as a preeminent neuroscience institute. The former Junior Faculty Development Program continues to provide mentoring and career development support to early career faculty with particular focus on their fifth through seventh years at MIT, a critical time in progression to tenure, through Junior Faculty Awards, currently supporting Gloria Choi and Steve Flavell. The Picower Institute Catalyst Program (PICP) is a gift matching fund that leverages donations to jump-start research partnerships with private sponsors. The million dollars donated to PICP has yielded $29 million of additional, vital research support. Together, JPB support has allowed us to achieve breakthroughs in 3D brain mapping, understanding how synapses encode the information we've learned, and identifying brain circuits and cellular disruptions that are key to various brain illnesses. Investing in basic research has the potential to save lives and generate economic impact.

As part of MIT's mission to help build a better world, PILM continued to host the Alana Down Syndrome Center, an innovative research, technology, and fellowship endeavor to support individuals of all abilities, including Down syndrome, created in 2019 with a $28.6 million gift from the Alana Foundation—a nonprofit organization started by Ana Lucia Villela of São Paulo, Brazil. This year the foundation continued its support with $5.9 million to MIT. Eight annual fund donors joined to help build upon the partnership (see also the Research Initiatives section).

Significant efforts and development resources continue to be directed toward our major cross-institutional health research initiative on brain aging and related cognitive decline: the Aging Brain Initiative (ABI) at MIT. Led by Li-Huei Tsai, PILM director, with seven founding faculty members and Michael Sipser, the dean of the School of Science, the ABI remains a top health priority in MIT's Campaign for a Better World. Several private, in-person or Zoom meetings raised awareness and increased the visibility of the effort this past fiscal year. A webinar hosted by MIT's Alumni Association on June 25 presented new Alzheimer's work that Tsai's lab published in *Nature Medicine* to 747 registered

individuals, including major donors to the ABI and the Picower Institute and several influential individuals from around the world, many of whom had not been connected to the work. On March 12, Priscilla King Gray, spouse of past MIT president Paul Gray, generously offered a challenge gift of $10,000 if 40 individuals gave to the ABI Fund during MIT's Pi Day. Indeed 122 individuals rose to the challenge enabling a total of $28,993 for the initiative. The ABI also completed its first Aging Brain Update, a newsletter sent to donors highlighting accomplishments of the year, and an annual update letter from the director thanking individuals for their contributions on December 19.

Notable new commitments for the ABI included a generous new $700,000 pledge from Robert and Renée Belfer and a matching payment of $577,500 from the Ludwig Family Foundation to support a translational program of Alzheimer's research through 2020. The Eleanor Schwartz Charitable Foundation pledged a new $500,000 gift and new six-figure commitments to Alzheimer's research were given by MIT alumni Lester Gimpelson '57 and David and Dagmar Dolby. After Tsai's visit to Madrid and participation in the Nobel Prize Dialogue in May 2019, the ABI received a $900,000 pledge to support three postdoctoral fellowships with preference for exceptional European candidates in brain aging research. The Belfer family also continued support for other breakthrough Alzheimer's research at the Institute through the Neurodegeneration Consortium, a collaboration among MIT, The University of Texas MD Anderson Cancer Center, and Mount Sinai School of Medicine.

The Picower Institute had planned to host our biennial daylong symposium, Early Life Stress and Mental Health, to honor Barbara Picower and the JPB Foundation on May 12, 2020. This event normally attracts more than 400 scientists, educators, students, foundations, and other interested outside groups to discuss how early life adversity, including inequality, affects health outcomes over a lifespan. However, due to the COVID-19 pandemic, the event is rescheduled for May 11, 2021.

Other notable gift pledges to the Picower Institute include $1.3 million from the Simons Foundation and $600,000 from the Nancy Lurie Marks Family Foundation to support autism research in the Choi Lab. Additionally, this year PILM received generous five-figure gifts from many individuals and an increase in smaller annual fund gifts from MIT alumni and new unaffiliated donors, all of which have proved vital to the Picower Institute's mission of advancing brain research.

Media Recognition

The Picower Institute has attained a distinguished international reputation as a neuroscience research leader. Faculty scholarly excellence shows in their publication records. In the reporting year, PILM faculty published 73 articles in such journals as *Nature*, *Cell*, *Neuron*, *Cell Reports*, *Nature Neuroscience*, and *Nature Communications*.

Often working with the MIT News Office, Picower Institute posted 30 press releases in FY2020 and 13 feature stories on its website and growing social media feeds. PILM research, commentary, and people were reported on more than 80 times by news sources, including NBC News, BBC, *Washington Post*, *Guardian*, *Discover*, *Scientific American*, *Popular Mechanics*, *Science News*, *Quartz*, Gizmodo, and LiveScience.

Programs and Activities

Collaboration among disciplines is integral to the Picower Institute's research philosophy. To facilitate collaboration, PILM holds many formal lectures, conferences, and workshops, as well as informal events. These activities bring Picower researchers and the MIT neuroscience community together with other neuroscientists and practitioners to exchange research findings, facilitate cross-disciplinary collaborations, and explore the potential research advances regarding learning and memory mechanisms.

Picower Institute colloquia bring the highest caliber of researchers from universities throughout the world to share their findings and experiences with the MIT community and to create working relationships with PILM members. During the past year, speakers included Vanessa Ruta of Rockefeller University and Thomas Clandinin of Stanford University. After other colloquia for the semester were canceled due to the COVID-19 pandemic, Picower faculty members Earl Miller and Mriganka Sur delivered virtual seminars in May that drew approximately 500 attendees each.

Plasticity refers to the changes in our synapses every time we learn, experience, or remember anything new. Picower Plastic Lunches refer to a series of informal talks during the academic year where PILM postdocs and graduate students share their latest, often prepublication, research with Building 46 colleagues. The series provides an opportunity for participants to improve their presentation skills, foster collaborations, and build new relationships across disciplines and between laboratories.

Picower Power Lunches are monthly faculty lunches that allow faculty and guest speakers to informally relate recent research findings or present new ideas.

The Picower Institute hosted the annual fall symposium Neural Mechanisms of Memory and Cognition on October 16. Experts from around the globe gathered to share their latest research. The event was well attended with about 450 registrants.

On November 6, the Picower Institute hosted the Alana Down Syndrome Center's inaugural symposium, Translational Research in Down Syndrome. Experts in the field delivered informative talks discussing the latest basic and clinical research on Down syndrome and provided an opportunity for attendees to network with Boston-area researchers. The half-day event was nicely attended and livestreamed to a large international audience.

Held annually, the Picower Lecture honors and recognizes the generous support of the Picower Foundation. Each lecture features work of a current leader in the area of brain research. This year's lecture by Catherine Dulac of the Howard Hughes Medical Institute and Harvard University was postponed to spring 2021, due to the COVID-19 pandemic.

Together with the School of Science, the Picower Institute continued the Aging Brain Seminar Series, which focuses on fundamental and translational research. Speakers were Bing Ren of the University of California at San Diego and Jerold Chun of Sanford Burnham Prebys Medical Discovery Institute. An additional ABI seminar with Randy Buckner of Harvard University was canceled due to COVID-19. It will be rescheduled.

There were also several special seminars during the academic year. Speakers included Yoshiyuki Kubota of the National Institute for Physiological Sciences, Japan. An additional lecture with Jin Hyung Lee of Stanford University was canceled due to COVID-19.

After the close of the academic year, the Picower Institute normally hosts an annual retreat for its community members. Like other spring events, the retreat was canceled due to COVID-19.

Originally targeted to the Picower Institute's postdoc community, but now a Building 46-wide association, the Postdoc Association provides resources to support activities that build community and enrich interactions between postdoctoral colleagues and future associates. Throughout the past year, the association convened a series of informal talks, educational seminars, and social events.

Research programs enabled by philanthropic support from the JPB Foundation and the RIKEN Institute afford us a unique research environment to support our faculty, lab members, and administrative team. The programs include the Clinical Collaborative Fellowship; Picower Neurological Disorder Research Fund; Picower Fellows program; Symposium Fund; Picower Institute Innovation Fund; the RIKEN-MIT Center for Neural Circuit Genetics; and the Catalyst Program (see also the Resource Development section).

Research Initiatives

RIKEN-MIT Laboratory for Neural Circuit Genetics

Established in April 2008, the RIKEN-MIT Laboratory for Neural Circuit Genetics is directed by Picower Professor of Biology and Neuroscience Susumu Tonegawa, and jointly sponsored by the RIKEN Center for Brain Science in Japan and MIT. The laboratory's objective has been to deepen our understanding of molecular, cellular, circuits, and brain systems mechanisms underlying learning and memory, by using a combination of new research tools and technology, such as spatially and temporally restricted transgenic mice, virus vector-based gene introduction, optogenetics, pharmacogenetics, calcium imaging, tetrode recordings, and sophisticated rodent behavioral paradigms. The laboratory's focus has been deciphering cellular and neural circuit mechanisms underlying the encoding, consolidation, and retrieval of episodic memory. Uncovering the fundamental mechanisms operating in the healthy brain aids understanding of how these mechanisms go astray in disease. The RIKEN-MIT agreement funds the activities of the laboratory, and will primarily support the Tonegawa research group for the next three years (as of April 2020). In the past year, the Tonegawa Lab published two papers on fear extinction and the discovery of new event code in the hippocampus in major journals (i.e., *Nature Neuroscience* and *Neuron*), and a commissioned a *Science* review on the history and role of engram theory. All of these publications were partially funded by this collaboration.

iPS Core Facility

Launched in 2010, the iPS Core Facility (ICF) integrates research goals of the Picower and McGovern Institutes and the Department of Brain and Cognitive Sciences to create human and animal cell models of disease. The various laboratories have expertise and

experience with different experimental protocols that, when combined in a collaborative manner to the study of human cells, result in accelerated progress in this novel, dynamic, and competitive field. The advent of human-induced pluripotent stem cells (iPSCs) heralds a new generation of clinical and basic research into disorders. Patient-derived skin fibroblast cells are reprogrammed into iPSCs, allowing researchers to directly examine a wide variety of diseases in addition to studying gene variants in patient populations. This core facility has rapidly become essential to studies of autism, psychiatric disease, Alzheimer's, and many neurodegenerative diseases. The ICF is accessible to users at all hours. Shared equipment is available with a reservation system. In FY2014 the iPS facility became a fee-for-service facility, open to other MIT users and to users external to MIT.

The ICF is equipped for the specialized production, maintenance, expansion, preservation, and distribution of human fibroblasts, iPSC lines, iPS- and ES-derived neuronal progenitor cells, iPS- and ES- derived neurons, induced neuronal cells, and neural organoids. Approximately 1,600 square feet house three tissue culture areas; one room is dedicated for viral work with iPS and ES cells as BL2plus practice for higher safety protocol, and two tissue culture areas are for maintenance, expansion, and general handling of nonviral work with iPS and ES cell culture with BL2 safety practice. There are 15 biosafety cabinets, 28 CO_2 incubators including three of the three-gas incubator that allows controlling of hypo- or hyper-O_2 concentration, and bench areas. There are four biosafety cabinets equipped with microscopes for observation and handling of cells in a clean and protected environment. The ICF has produced more than 70 patient-specific iPSC lines from donors with schizophrenia, bipolar disease, depression, Rett syndrome, Alzheimer's, and Down syndrome, as well as from healthy people. Isogenic iPSC lines are also generated/used for various disease model research.

Supervisor Tak Ko has set up an orientation program and trainings to educate faculty and potential users. Since its inception, more than 25 MIT researchers have used the facility. Moreover, collaboration with researchers outside of MIT has continued. Noteworthy interactions with the Broad Institute include applying platforms with pluripotent stem cells for the studies: "A cloud-based pipeline for DIA data analysis enables phosphosignaling studies in genetic risk variants of Alzheimer's disease," and "multiproteomics characterization of diverse brain cell types using low-input phosphoproteomics and global chromatin profiling." Biotech industries also inquire about iPSC culture service and Cambridge biotech company Solid Biosciences sent a researcher to learn basic iPSC maintenance techniques and cardiomyocyte differentiation procedures. Using data from the ICF, many prominent articles have been published in scholarly journals, including *Cell Systems*, *Neuron*, *Nature*, *Nature Neuroscience*, *PLoS One*, and *Molecular Psychiatry*.

MIT researchers have often leveraged ICF capabilities to receive external funding. Sources and related projects included the Alana Foundation: Alana USA Fund; National Institute of Health (NIH): The cdk5/p35 kinase; Broad, NIH: There and Back Again—Epigenetic Reinforcement of Cellular Signaling Stages; MD Anderson: The Neurodegeneration Consortium; Cure Alzheimer's: Circuits Consortium; NIH: Mechanisms Underlying DNA Double Strand Break Response in Alzheimer's Disease and Frontal Temporal Dementia; NIH: Epigenomic, Transcriptional and Cellular

Dissection of Alzheimer's Variants; NIH: Dissection of Endosomal Trafficking Mechanisms in Alzheimer's Disease; NIH: Elucidating the Molecular Mechanisms of Neuropsychiatric Symptoms in Alzheimer's Disease; NIH: Single-Cell Transcriptional and Epigenomic Dissection of Alzheimer's Disease and Related Dementias; NIH: Construction of an Integrated Immune—Vascular Brain—Chip as a Platform for the Study, Drug Screening, and Treatments of Alzheimer's Disease; NIH: Development of PU.1 Inhibitory Modulators as Novel Therapeutics for Alzheimer's Disease; MIT PILM: 2020 PIIF Engineering Grant; Down Syndrome Research Fund.

3D Imaging Core Facility

In 2020, PILM created a shared 3D imaging core facility after the purchase of a LifeCanvas light sheet microscope. The real value of light sheet microscopes is their ability to image large tissues, and one of the most powerful applications in Picower is the ability of the LifeCanvas system to very comfortably image whole mouse brains. The system provides superior axial resolution with a consistent light sheet thickness, regardless of detection magnification. Additionally, it provides high accuracy Z-stage motion (20nm and a large range of motion for larger samples). The facility is available to all Picower labs and accessible for use 24 hours a day, seven days a week.

The Aging Brain Initiative

The bold goals of the Aging Brain Initiative (see also the Resource Development section) 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 to address this global health imperative. The program brings MIT's leading memory and neurobiology researchers together with engineers, computer scientists, economists, urban planners, social policy experts, clinicians, and industry partners to think creatively about brain aging and to collectively tackle ambitious ideas that have not been pursued. High-risk flagship projects include a whole-systems perspective extending beyond the traditional clinical pathology and genetic approaches of today to include vital aspects of the challenges, such as understanding memory loss and developing technologies for improved study and care. Frequent multidisciplinary discussion forums and seminars enable open sharing of data and accelerated development of ideas for growth into new areas.

ABI director Tsai was invited to give a plenary session at the 2019 Society for Neuroscience Annual Meeting, covering her lab's translational ABI-sponsored Alzheimer's work. Tsai and a member of her lab also presented to a well-attended alumni association webinar on Alzheimer's disease.

An Aging Brain Initiative Fellows program was established this fiscal year through a generous donation from the "La Caixa" Foundation' and launched in spring 2020. It will fund three postdoctoral fellows from MIT as they pursue aging brain related projects.

The ABI continues to focus on approaches that consist of project- and team-based, immediately implementable research to help us understand both healthy and unhealthy brain aging, and to develop real-world solutions that reduce cognitive decline, aid home care, and point toward a cure for diseases, such as dementia. Research centers

around MIT's strengths, such as: big data approaches; circuit and systems therapeutic approaches, including noninvasive stimulation regimens and ways to restore memories; personalized approaches to treatment through new models of disease; and uncovering mechanisms supporting healthy aging and resilience.

In FY2020, ABI researchers published major advancements. In a *Nature Medicine* publication, ABI founders Li-Huei Tsai and Manolis Kellis described a model of the blood-brain barrier in a dish to study risk factors for Alzheimer's disease. Tsai also published work with ABI member Kwanghun Chung that used 3D mapping to trace pathological markers of Alzheimer's disease. Myriam Heiman published two works studying the effects of mutant Huntington's disease protein on cell health. ABI founder Ed Boyden and member Mark Bear developed a tool for imaging neural activity in the brains of awake animals. The ABI team of Tsai, Emery N. Brown, and Boyden proceeded with clinical trials at MIT of a noninvasive light and sound device for treating Alzheimer's disease. The group will complete their first trial in Alzheimer's patients soon and are planning other trials for prevention of Alzheimer's disease in collaboration with clinicians at Massachusetts General Hospital, and possible expansion into other neurodegenerative disorders.

The Alana Down Syndrome Center

In March 2019, MIT launched the virtual Alana Down Syndrome Center (ADSC), hosted by the Picower Institute. The ADSC aims to deepen knowledge about Down syndrome (DS) and to improve health, autonomy, and inclusion of people with this genetic condition.

The ADSC is multidisciplinary, spanning labs and programs across MIT, and engages the expertise of scientists and engineers to increase understanding of the biology and neuroscience of DS.

The mission is to produce research and technology to give people with disabilities the possibility of developing greater social and practical skills, in order to enhance their participation in the educational system, in the workforce, and in community life.

The ADSC pursues progress in the following three main ways:

- Research investigates mechanisms and potential therapeutic interventions in two main areas: brain circuits and systems, and cellular mechanisms and genetic variation. With these approaches, the team strives to improve understanding of why individuals with DS experience functional differences and the best ways to address them.
- In a program called Technology to Improve Ability, with the Deshpande Center at MIT, creative minds across MIT are encouraged and supported through grants to design and develop technologies that can improve life for people with different intellectual abilities or other challenges.
- Through postdoctoral and graduate fellowship programs, the center builds a pipeline of talent to increase the number of scientists who are enthusiastic about and skilled in DS research. In FY2020, five new fellows (two graduate students

and three postdocs) joined the ADSC fellowship program. Trained in the center's labs with advanced and innovative techniques, this class of fellows, as well as undergraduate students who join these projects, have the potential to amplify the center's discoveries throughout their careers.

Faculty Research Summaries

Picower Institute faculty research areas are summarized below:

Mark Bear

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

How is the brain modified by experience, deprivation, and disease?

Our overarching interest is in the question of how experience and deprivation modify synaptic connections in the brain. Experience-dependent synaptic plasticity is the physical substrate of memory, 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 and contributes to their symptoms.

Our major efforts to address this question focus 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 (MD) during childhood. MD sets in motion a stereotyped choreography of synaptic modification whereby the deprived-eye inputs to visual cortex rapidly lose strength and, with a delay, the open-eye 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, 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 amblyopia treatment.

The hippocampus is a cortical structure critical to forms of learning and memory. The simple cellular architecture of the hippocampus makes it especially amenable to electrophysiological investigations of synaptic plasticity. In the early 1990s, we 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 hippocampus. The hippocampus is therefore an excellent preparation 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 also to understanding the basis of hippocampus-dependent memory storage and diseases of cognition.

In the course of studying LTD, we made a discovery that has 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 mRNAs at synapses. In studying this type of synaptic plasticity, we discovered that protein synthesis (and LTD) downstream of mGluR5 is exaggerated in the mouse model of fragile X syndrome. Human fragile X is caused by the silencing of the FMR1 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 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. Results of ensuing human clinical trials based on the strength of this science indicate that treatments can be developed to substantially benefit this patient population. The mGluR theory has contributed to a major paradigm shift that genetic diseases of brain development, historically viewed as untreatable, may be ameliorated or corrected with appropriate therapy.

Current work in the laboratory 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. We primarily study mouse models, and we use a broad range of methods that include but are not limited to brain slice electrophysiology and biochemistry, in vivo electrophysiology and two-photon functional and structural imaging, and behavioral analysis. Our lab is *question* oriented rather than *method* oriented. We will apply any technology necessary to address the questions of greatest interest.

Emery Brown

Emery Brown is a Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience, Institute for Medical Engineering and Sciences, Department of Brain and Cognitive Sciences.

Neural signal processing algorithms

Recent technological and experimental advances in the capabilities to record signals from neural systems have led to an unprecedented increase in the types and volume of data collected in neuroscience experiments and hence, in the need for appropriate techniques to analyze them. Therefore, using combinations of likelihood, Bayesian, state-space, time-series and point process approaches, a primary focus of the research in my laboratory is the development of statistical methods and signal-processing algorithms for neuroscience data analysis. We have used our 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 fMRI time-series
- characterize the spiking properties of neurons in primary motor cortex
- localize dynamically sources of neural activity in the brain from EEG and MEG 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 heart beats in physiological and pathological states
- de-noise two-photon in vivo imaging data

Understanding general anesthesia

General anesthesia is a neurophysiological state in which a patient is rendered unconscious, insensitive to pain, amnestic, and immobile, while being maintained physiologically stable. General anesthesia has been administered in the United States for more than 160 years and 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. My laboratory is using a systems neuroscience approach to study how the state of general anesthesia is induced and maintained. To do so, we are using fMRI, EEG, neurophysiological recordings, microdialysis methods, and mathematical modeling in interdisciplinary collaborations with investigators in BCS, the MIT/Harvard 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; create safer, site-specific anesthetic drugs; and to develop better neurophysiologically-based methods for measuring depth of anesthesia.

Gloria Choi

Gloria Choi is a Samuel A. Goldblith Career Development Assistant Professor, Department of Brain and Cognitive Sciences

The primary goal of my research program is to elucidate the mechanisms through which the immune system modulates neural circuit function, ultimately shaping animal behavior. We were initially intrigued by the observation that viral infection during pregnancy correlates with increased frequency of neurodevelopmental disorders in offspring. Indeed, mice prenatally subjected to maternal immune activation (MIA) display defects in their interactions with conspecifics and develop perseverative behaviors, which we have shown to require the activity of maternal T helper 17 (Th17) cells and the cytokine interleukin (IL)-17a they secrete. We further showed that maternally-derived IL-17a acts during development through the canonical IL-17 receptor a (IL-17Ra), at the level of cortical neurons in the fetal brain. IL-17Ra activation in the fetal brain leads to a cortical phenotype that is preferentially localized to the dysgranular zone of the primary somatosensory cortex (S1DZ) in adult MIA offspring. Loss of parvalbumin^{+} inhibitory interneurons in the S1DZ is accompanied by increased neural activity, which results in MIA-induced abnormal behaviors. This neuroimmune interaction across the maternal-fetal boundary is further modulated by the maternal gut microbiota. Thus, IL-17Ra

activation in the fetal brain by maternal IL-17a leads to perturbation of cortical activity and results in behavioral deficits that emerge later in the life of offspring.

Th17 cells represent only one of the many immune cell types that secrete cytokines. Various adaptive and innate immune cell populations are recruited under different infectious conditions, and the brain likely is endowed with molecular and cellular mechanisms to respond to these signals. Uncovering the precise relationship between immune conditions and the neural circuits and behaviors that they modulate will provide access to novel pathways that facilitate the exchange of information between the nervous and immune systems both in healthy and diseased states. Understanding this complex language will also provide the necessary platform to devise therapies to treat neurodevelopmental and neurological disorders whose causes are rooted in a dysregulated immune system.

Kwanghun Chung

Kwanghun Chung is a Picower Associate Professor of Neuroscience, Department of Brain and Cognitive Sciences, Department of Chemical Engineering, Institute for Medical Engineering and Sciences.

Kwanghun Chung leads an interdisciplinary research team devoted to developing and applying novel technologies for holistic understanding of large-scale, complex biological systems. In the past year, he led several, large multi-PI projects, including a $9 million NIH human brain mapping project and a $5 million NIH reusable antibody development project, to apply his technologies for mapping and studying the human brain. Additionally, his group has active collaborations with many researchers at MIT, Broad Institute, MGH, and Harvard to study various neurological disorders, such as autism spectrum disorder and Alzheimer's disease. He has traveled extensively, including visits to Caltech, Johns Hopkins University, and Georgia Tech, to speak about his group's technologies and their applications. Professor Chung taught 10.302 Transport Processes, and HST.562J Pioneering Technologies for Interrogating Complex Biological Systems. Professor Chung continued serving as a chief scientist for the startup LifeCanvas Technologies, which aims to advance the adoption and usage of the technologies developed by the Chung Lab at MIT.

Steven Flavell

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

Action potentials and synaptic transmission occur over the timescale 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 timescales. 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.

Flavell's recent studies have identified a neuromodulatory circuit that generates two opposing behavioral states that C. elegans animals generate while foraging for food. This work demonstrates how neuromodulators like serotonin and various neuropeptides supplement fast motor circuits with slow temporal dynamics, organizing behaviors into long-lasting states. Additionally, a 2019 study illuminated how neural circuits can incorporate information about food ingestion, such that neural activity patterns can be modulated by gut-brain signaling. The discovery that ASICs mediate the detection of gut bacteria is particularly exciting and the subject of a new line of studies in the Flavell Lab.

Ongoing work in the Flavell Lab continues to ask fundamental questions about how behavioral states are generated and how environmental cues influence state generation: For instance, what circuit-wide patterns of activity define the stable configurations for different behavioral states? How are these patterns stabilized by neuromodulators like serotonin? Toward this end, his lab constructed a microscope suitable for whole-brain calcium imaging and used this new technology to characterize large-scale neural activity patterns associated with distinct behavioral states. The Flavell Lab is also combining their use of whole-brain neural recordings with genetic approaches to characterize the functional organization of the serotonergic system at the scale of a whole brain for the first time. Additional studies in the Flavell Lab address neural encoding of satiety state, associative memories, and more.

Myriam Heiman

Myriam Heiman is a Latham Family Career Development Associate Professor of Neuroscience, Department of Brain and Cognitive Sciences, Core Member of the Broad Institute.

The most common neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's, each display distinct clinical presentations. The basis of these distinct clinical presentations is 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, as we 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. We are using innovative approaches to address these long-standing questions of selective vulnerability that have remained open questions in the field for decades. In the past year, our cell type-specific molecular profiling studies in Huntington's disease (HD) models and now human HD brain tissue have revealed that mitochondrial function is perturbed early on in the most vulnerable cell types in HD, and that this mitochondrial dysfunction leads to the release of mitochondrial nucleic acids and innate immune activation in neurons. In a separate line of research, using a genome-wide, unbiased in vivo shRNA and CRISPR genetic screening methodology, we have identified a number of genes essential for neuronal viability in vivo, including the gene Nme1, which is protective against mutant Huntingtin protein aggregation. We are actively pursuing genetic and small molecule means to boost this gene's function in the brain. In addition to these HD-focused studies, our other studies have suggested that the brain circuitry that connects the

prefrontal cortex to the ventral striatum (two brain areas implicated in schizophrenia) is strengthened by chronic antipsychotic drug treatment. As this circuitry is also involved in resilience to compulsive cocaine use, in a collaborative study with NIH researchers we have recently shown that chronic antipsychotic drug treatment can modulate resilience to compulsive cocaine use, a finding that we believe will have clinical relevance in the treatment of substance use disorder. Finally, we have recently undertaken an extensive profiling of the molecular characteristics of the cells that comprise the human blood-brain-barrier (BBB), as these cell types have been implicated in many neurodegenerative diseases, and we have already identified several key human BBB-specific characteristics.

Troy Littleton

Troy Littleton is a 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 to generate plasticity. The lab uses drosophila to characterize these basic synaptic mechanisms and how they are dysfunctional in models of epilepsy, Huntington's disease, and autism. Neurotransmitter release from presynaptic terminals is the primary mechanism of synaptic communication and is mediated by fusion of synaptic vesicles with the plasma membrane at specific sites known as active zones. Ca^{2+} influx through voltage-gated Ca^{2+} channels function as the trigger to activate the fusion. The majority of vesicles fuse during a synchronous phase that occurs within a few milliseconds of Ca^{2+} entry. Many synapses also have an asynchronous component that results in vesicle release over hundreds of milliseconds. Changes in the kinetics and amount of synaptic vesicle fusion also occur during high frequency stimulation, resulting in short-terms of plasticity like facilitation or depression, depending on the synapse. Defining the molecular machinery and Ca^{2+} sensors that regulate the distinct modes and kinetics of synaptic vesicle release is essential for understanding synaptic transmission. Recent work in the lab has begun to define the molecular underpinnings of these forms of release and plasticity, including the discovery that the Ca^{2+} sensor Synaptotagmin 7 negatively regulates synaptic vesicle fusion to allow facilitation to occur at synapses.

Earl Miller

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

The overarching goal of 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 lab has developed (and shares) technology and techniques for recording from many separately movable, acutely inserted electrodes, which allows 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.

Elly Nedivi

Elly Nedivi is a William R. (1964) and Linda R. Young Professor of Neuroscience, Departments of Brain and Cognitive Sciences and Biology.

The Nedivi Lab 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), we have elucidated the neuronal and synaptic function of two previously unknown CPGs, CPG15 and CPG2, showing that each provides unique insight into diverse aspects of plasticity mechanisms. Both molecules have subsequently become well known, CPG15 (later named neuritin) as an extracellular ligand with multiple roles (also outside the nervous system), and CPG2 as a product of SYNE-1, one of the best genetic hits for bipolar disorder. Motivated by the large number of CPGs that affect neuronal structure, we have a long-standing collaboration with Peter So's lab in the Department of Mechanical Engineering at MIT to develop multiphoton 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

Mriganka Sur is a Paul E. Newton Professor of Neuroscience, Department of Brain and Cognitive Sciences, Director of the Simon's Center for the Social Brain.

The Sur Lab studies the development, plasticity, and dynamics of circuits in the cerebral cortex of the brain. The developing brain requires a genetic blueprint but is also acutely sensitive to experience and the environment. The adult brain responds to external stimuli and modulates these responses by internal states, such as attention, through dynamic changes in information transmission and processing.

Brain processing is enabled by local and long-range cortical circuits, which are wired during development by mechanisms of plasticity, and change during adulthood by mechanisms of learning and memory. Abnormal wiring of synapses and circuits lies at the core of many brain disorders. The goal of our laboratory is to understand long-term plasticity and short-term dynamics in circuits of the developing and adult cortex, and utilize this understanding to discover mechanisms underlying disorders of brain development.

Susumu Tonegawa

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

Our lab continues to focus on 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 hold 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; IT complex for visual memory; cerebellum for motor memory), none of these studies causally identified a specific

neuronal population as the holder of a specific memory. We 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/chemical changes in the brain network (or 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/chemical changes are induced in them; and third, their subsequent reactivation by recall cues induces behavioral recall.

Having published a milestone paper showing the sufficiency and necessity of an engram for a specific memory, my lab continues to elucidate engram mechanisms for various types of memory (e.g., emotional, social), including consolidation and retrieval, and we also are evaluating applications of such knowledge that could facilitate the amelioration of human brain disorders, such as Alzheimer's disease and PTSD. In the given year, we have focused specifically on several important questions and goals that are critical for a better understanding of memory in the mammalian brain: What is the role of engram cell excitability in memory retrieval; characterizing the role/mechanism for prefrontal cortex (mPFC) engrams in memory consolidation; determining the role of hippocampal vCA1 neurons in social memory disorders; elucidating the role of the basolateral amygdala in inducing and antagonizing emotional memory; making a landmark discovery of a new code in the hippocampus (event code); the neurobiology of transitivity knowledge using olfactory-based engrams; and dynamic circuit representation of time and space within the hippocampus.

Li-Huei Tsai

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

Our laboratory is interested in elucidating the pathogenic mechanisms underlying neurological disorders that impact learning and memory. We take multidisciplinary, network-level approaches to decipher the molecular, cellular, and circuit basis of neurodegenerative disorders.

Transcriptomic and epigenomic analysis of brain disorders

We are currently interested in understanding the transcriptomic and epigenomic landscape in the major brain cell types in both normal physiological brain function and under pathological disease states. In parallel work, we are examining the role of genomic integrity in the development of age-related neurological disorders.

Systems level analysis of neurodegeneration

Cognitive deficits that occur in neurodegeneration may arise from an accumulation of altered cellular processes that lead to disruptions in neural circuits and network connectivity. In particular, oscillations in the gamma frequency range (between 30 and

80 Hz) are associated with higher order brain functions, and may be disrupted in the early stages of Alzheimer's disease in human patients as well as in mouse models. We are thus interested in applying circuit manipulations to ameliorate cognitive deficits in Alzheimer's disease. Through the targeted application of optogenetic and chemogenetic tools, we also aim to manipulate the activity of specific neural populations and circuits to gain insights at the intersection of pathology, network activity, and behavior. Additionally, we are mapping out the sequential, temporal, and spatial disruptions of neural circuits by the deposition of amyloid and aggregated tau protein in Alzheimer's disease, to identify nodes of vulnerability and to understand how these pathologies propagate throughout the brain.

Using human-induced pluripotent stem cells and tissue bioengineering to model Alzheimer's disease and Down syndrome

Our lab has generated numerous induced pluripotent stem cell lines by reprogramming fibroblasts from healthy individuals, as well as from late onset sporadic Alzheimer's disease, early onset familial Alzheimer's disease, and Down syndrome patients. To assess the phenotypic consequences of disease-associated genetic variants, we additionally apply the CRISPR/Cas9 genome editing technique to create isogenic cell lines, as well as genome-engineering approaches, such as the dCAS9 system to examine the impact of noncoding genetic variants of Alzheimer's disease on gene expression. In addition to conventional 2D cultures, the Tsai Lab is also developing and utilizing complex culture systems in 3D and with multiple cell types in co-culture. Using techniques of bioengineering combined with multiphoton deep imaging, optogenetics, and electrophysiology, we can recapitulate and study complex in vitro models of human brain tissue.

Matthew Wilson

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

Work in the Wilson Lab focuses 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, and 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. Recent work has discovered new links between brain areas that have been associated with memory and mood that highlight the importance of movement in cognition and planning. We have also developed new methods for large-scale optical imaging of brain activity in freely behaving animals and have used these tools to identify novel correlates of memory formation during behavior and sleep.

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