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, 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 Brown received the Carnegie Mellon's Dickson Prize in Science; a Doctor of Science (Honoris Causa) from the University of Southern California; and was elected a member of the board of trustees on the John Simon Guggenheim Memorial Foundation.

Assistant Professor Steven Flavell was named the Lister Brothers Career Development Professorship from the School of Science. Flavell received the Brain and Cognitive Sciences (BCS) Award for Excellence in Graduate Mentoring and the National Science Foundation (NSF) CAREER Award.

Professor Earl Miller received the George A. Miller Prize in Cognitive Neuroscience and the BCS Award for Excellence in Graduate Teaching.

Professor Elly Nedivi was elected as a member-at-large of the selection committee on the American Association for the Advancement of Science (AAAS) and named the William R. (1964) & Linda R. Young Professor of Neuroscience.

Professor Li-Huei Tsai received the Hans Wigzell Research Foundation Science Prize.

Mat Victor (postdoctoral fellow in the Tsai Lab) received the Howard Hughes Medical Institute (HHMI) Hanna H. Gray Fellowship.

John Tauber (graduate student in the Brown Lab) received the Angus MacDonald Award for Excellence in Undergraduate Teaching.

Jungsoo Kim (graduate student in the Flavell Lab) received the BCS Award for Excellent Teach Assistant (TA) of Undergraduates.

Lisandro Martin (technical associate in the Bear Lab) received the BCS Walle J. H. Nauta Award for Outstanding Research in Brain and Cognitive Sciences.

Graduate students Joyce Wang (Bear Lab), Scarlett Barker (Tsai Lab), Nicole Aponte-Santiago (Littleton Lab), Karen Leopold Cunningham (Littleton Lab), and Karen Guadalupe Cruz (Sur Lab) were all named 2019 Graduate Women of Excellence Honorees.

Research Advances

Clinicians have long had the goal of separating analgesia from anxiety when using deep brain electrical stimulation of the periaqueductal gray (PAG) for difficult-to-treat pain. Professor Brown and collaborators have shown that selective activation of dopamine (DA) neurons within the PAG produces analgesia without other behavioral effects, while stimulating glutamatergic neurons mediates stress-induced anxiety and analgesia. Results suggest that DA agonists may represent a novel class of analgesic drugs and elucidate target neurons that could mediate their effect. (Taylor et al., *eNeuro,* 2019)

Anesthetics have profound effects on the brain and central nervous system. Vital signs, along with the electroencephalogram (EEG) and EEG-based indices, are commonly used to assess the brain states of patients receiving general anesthesia and sedation. Important information about the patient's arousal state during general anesthesia can also be obtained through use of the neurologic examination. A new article reviews the main components of the neurologic examination focusing primarily on examining the brainstem, detailing the components that are most relevant for patient management during induction, maintenance, and emergence from general anesthesia. The examination is easy to apply and provides important complementary information about the patient's arousal level that cannot be discerned from vital signs and EEG measurements. (Reshef et al., *Anesthesiology,* 2019)

Spectral properties of the EEG are commonly analyzed to characterize the brain's oscillatory properties in basic science and clinical neuroscience studies. The spectrum is a function that describes power as a function of frequency. To date, inference procedures for spectra have focused on constructing confidence intervals at single frequencies using large, sample-based analytic procedures or jackknife techniques. These procedures perform well when the frequencies of interest are chosen before the analysis. When these frequencies are chosen after some of the data have been analyzed, the validity of these conditional inferences is not addressed. If power at more than one frequency is investigated, corrections for multiple comparisons must also be incorporated. To develop a statistical inference approach that considers the spectrum as a function defined across frequencies, researchers combine multitaper spectral methods with a frequency-domain bootstrap (FDB) procedure. The multitaper method is optimal for minimizing the bias-variance tradeoff in spectral estimation. The FDB makes it possible to conduct Monte-Carlo-based inferences for any part of the spectrum by drawing samples that respect the dependence structure in the EEG time series. Researchers show that their multitaper FDB procedure performs well in simulation studies and in analyses comparing EEG recordings of children from two different age groups receiving general anesthesia. (Kim et al., *IEEE Signal Processing Letters*, 2018).

Associate Professor Kwanghun Chung's lab developed two key technologies (SHEILD and eFLASH) for rapid and holistic phenotyping of complex biological systems. SHIELD simultaneously and globally protects tissue physicochemical properties while allowing multiscale molecular imaging (Park, *Nature Biotechnology*, 2019).

Additionally, the team developed a technology platform to 3D print and integrate synthetic vasculature networks with organoids, mini organs produced in vitro using patient-derived induced pluripotent stem cells (iPSCs), to address transport issues

that limit the power of the organoid systems. The team plans to submit four papers this year on the new technologies and their applications. They have continued to expand collaborations with biologists and clinicians at Harvard and MIT to apply the technologies for studying a broad range of biological questions.

Professor Flavell's lab discovered that Acid-Sensing Ion Channels (ASICs), a conserved class of ion channels, mediate the detection of gut bacteria by enteric neurons (Rhoades et al, *Cell*, 2019). This work further showed how enteric sensory neurons, upon detecting gut bacteria, signal to the brain via neuromodulator release to alter neural activity patterns.

Associate Professor Myriam Heiman's lab finished the first genome-wide shRNA and CRISPR screens for neuronal essential genes in the mammalian brain.

Menicon Professor of Neuroscience Troy Littleton's lab has made recent discoveries that provide key new insights into how glia cells communicate with and regulate their neuronal counterparts. Glial cells are well known to play structural and supportive roles for their more electrically excitable neuronal counterparts, but growing evidence indicates glial Ca^{2+} (calcium ions) signaling influences neuronal physiology on a rapid time scale. A single glia contacts multiple neuronal cell bodies, hundreds of neuronal processes, and tens of thousands of synapses. Additionally, glial cells can oscillate intracellular Ca^{2+} spontaneously and in response to neurotransmitters, which can trigger elevated activity in nearby neurons. These glial-neuron interactions suggest abnormally elevated glial Ca^{2+} might produce epilepsy. Indeed, work in the lab identified mutations in glial Ca^{2+} exchangers that trigger temperature-sensitive seizures in Drosophila (small fruit flies). Using genetic, electrophysiology, and imaging, the lab found that altered glial Ca^{2+} signaling in these mutants causes hyperactivation of calcineurin-dependent endocytosis, leading to removal of essential K^+ (potassium ion) channels that are required for controlling the K^+ buffering capacity of glia when neurons become highly active. Disruption of these pathways leads to enhanced neuronal excitability and seizures, providing new targets for future glial-based therapeutic modifiers of epilepsy. The lab recently published a new paper in this area (Weiss et al., *eLife*, 2019).

Professor Miller's lab made two noteworthy research breakthroughs. The Miller Lab presented a new model of working memory that explains how the brain holds information in mind (the "memory" part) and also executes volitional control over that (the "working" part) (Miller et al., 2019, *Neuron*). The lab also demonstrated improvements in cognition in humans via rhythmic brain stimulation (Widge et al., 2019, *Nature Communications*).

Professor Nedivi's lab explored a key feature of brain plasticity—the experience-dependent selection of optimal connections, implemented by a set of activity-regulated genes that dynamically adjust synapse strength and number. The activity-regulated gene CPG15/neuritin has been previously implicated in stabilization and maturation of excitatory synapses. The lab combined two-photon microscopy with genetic and sensory manipulations to dissect excitatory synapse formation in vivo, and examined the role of activity and CPG15 in dendritic spine formation, PSD95 recruitment, and synapse stabilization. Researchers found that neither visual experience nor CPG15 are required for spine formation. However, PSD95 recruitment to nascent spines and their

subsequent stabilization requires both. Further, cell-autonomous CPG15 expression is sufficient to replace experience in facilitating PSD95 recruitment and spine stabilization. These results, in press in *Cell Reports*, identify CPG15 as an activity-dependent spine stabilization signal that acts downstream of spine initiation, but upstream of PSD95 recruitment. To examine how CPG15, an extracellular GPI-linked protein can recruit the intracellular synaptic PSD95 scaffold, the lab followed up on proteomic studies showing a potential interaction between CPG15 and AMPA receptors, and showed that this interaction is direct. By elucidating CPG15's mechanism of action as an experience-dependent "selector" for spine stabilization and synapse maturation, the lab also clarified a sequence of molecular events in synapse formation, whereby AMPA receptor presence on immature spines precedes activity-dependent PSD95 recruitment, and subsequent spine stabilization and synapse maturation.

The Simons Center for the Social Brain Director and Newton Professor Mriganka Sur's lab achieved three research breakthroughs in AY2019:

- Active control of arousal by a locus coeruleus GABAergic circuit: Arousal responses linked to locus coeruleus noradrenergic (LC-NA) activity affect cognition. However, the mechanisms that control modes of LC-NA activity remain unknown. In this study, researchers reveal a local population of GABAergic neurons (LC-GABA) capable of modulating LC-NA activity and arousal. Retrograde tracing shows that inputs to LC-GABA and LC-NA neurons arise from similar regions, though a few regions provide differential inputs to one subtype over the other. Recordings in the LC demonstrate two modes of LC-GABA responses whereby spiking is either correlated or broadly anticorrelated with LC-NA responses, reflecting anatomically similar and functionally coincident inputs, or differential and non-coincident inputs, to LC-NA and LC-GABA neurons. Coincident inputs control the gain of LC-NA-mediated arousal responses, whereas non-coincident inputs, such as from the prefrontal cortex to the LC, alter global arousal levels. These findings demonstrate distinct modes by which an inhibitory LC circuit regulates arousal (Breton-Provencher et al., *Nature Neuroscience*, 2019).
- Functional imaging of visual cortical layers and subplate in awake mice with optimized three-photon microscopy: Two-photon microscopy is used to image neuronal activity, but has severe limitations for studying deeper cortical layers. The lab developed a custom three-photon microscope optimized to image a vertical column of the cerebral cortex > 1 mm in depth in awake mice with low (<20 mW) average laser power. Our measurements of physiological responses and tissue-damage thresholds define pulse parameters and safety limits for damage-free three-photon imaging. Researchers image functional visual responses of neurons expressing GCaMP6s across all layers of the primary visual cortex (V1) and in the subplate. These recordings reveal diverse visual selectivity in deep layers: layer 5 neurons are more broadly tuned to visual stimuli, whereas mean orientation selectivity of layer 6 neurons is slightly sharper, compared to neurons in other layers. Subplate neurons, located in the white matter below cortical layer 6 and characterized here for the first time, show low visual responsivity and broad orientation selectivity (Yildirim et al., *Nature Communications*, 2019).

- Atypical behavior and connectivity in SHANK3-mutant macaques: Mutation or disruption of the SH3 and ankyrin repeat domains 3 (SHANK3) gene represents a highly penetrant, monogenic risk factor for autism spectrum disorder, and is a cause of Phelan-McDermid syndrome. Recent advances in gene editing have enabled the creation of genetically engineered non-human-primate models, which might better approximate the behavioral and neural phenotypes of autism spectrum disorder than do rodent models, and may lead to more effective treatments. Researchers report CRISPR–Cas9-mediated generation of germline-transmissible mutations of SHANK3 in cynomolgus macaques (Macaca fascicularis) and their F1 offspring. Genotyping of somatic cells as well as brain biopsies confirmed mutations in the SHANK3 gene and reduced levels of SHANK3 protein in these macaques. Analysis of data from functional magnetic resonance imaging revealed altered local and global connectivity patterns that were indicative of circuit abnormalities. The founder mutants exhibited sleep disturbances, motor deficits and increased repetitive behaviors, as well as social and learning impairments. Together, these results parallel some aspects of the dysfunctions in the SHANK3 gene and circuits, as well as the behavioral phenotypes that characterize autism spectrum disorder and Phelan-McDermid syndrome.

In AY2019, Professor Susumu Tonegawa's lab showed that engram cell excitability is transiently increased following memory reactivation. This short-term increase of engram excitability enhances the subsequent retrieval of specific memory content in response to cues and is manifest in the animal's ability to recognize contexts more precisely and more effectively. These results revealed a hitherto unknown transient enhancement of context recognition based on the plasticity of engram cell excitability. They also suggested that recall of a contextual memory was influenced by previous but recent activation of the same engram. The state of excitability of engram cells mediates differential behavioral outcomes upon memory retrieval and may be crucial to survival by promoting adaptive behavior.

The team addressed the questions of how fear and fear extinction memories are stored in the amygdala by taking advantage of its previously published study. Namely, basolateral amygdala contains two genetically, functionally, and anatomically distinct neuronal subpopulations; R-spondin-2-expressing (Rspo2+) neurons that drive negative behaviors and have negative memory engram cells, whereas protein-phospotase-1-regulatory-inhibitor-subunit 1B-expressing (Ppp1r1b+) neurons drive positive behaviors and have positive memory engram cells. These two types of neurons suppress the activity of the other by feed-forward inhibition. In this study, researchers used various methods, including calcium imaging under a microendoscope, optogenetic activation and inactivation, c-Fos-tTA/TRE-opsin-based engram identification technology, activation of c-Fos in single cells, and aversive and appetitive valence behavioral paradigm. The lab demonstrated the fear extinction memory engram cells are formed in the Ppp1r1b+ BLA neuronal subpopulation which suppresses Rspo2+ fear neurons during the fear extinction training.

The brain codes continuous spatial, temporal, and sensory changes in daily experience. Recent studies suggest that the brain also tracks experience as segmented subdivisions (events), but the neural basis for the encoding of events remains unclear. Researchers

designed a maze for mice composed of four materially indistinguishable lap events, and report hippocampal CA1 neurons whose activity is modulated by lap number. This lap-specific "chunk code" is separate from the spatial code. The chunk code remains lap-specific even when the maze length is unpredictably altered within the laps, showing that this code treats segmented lap events as abstract and fundamental units of the experience. The chunk code is reused to represent lap events when the maze geometry is altered from a square to a circle, suggesting that this code promotes a transfer of abstract knowledge between similar experiences. The chunk code tracks events and may be a fundamental representation of experience.

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

- Manipulating neural oscillations with non-invasive sensory stimulation for Alzheimer's disease intervention: The activity of cells and neural circuits are altered in Alzheimer's disease (AD), and may represent a point of therapeutic intervention to affect disease progression. Previously, in an approach termed Gamma ENtrainment Using Sensory stimuli (GENUS), the lab found that neural oscillations in the gamma frequency range (30-90 Hz) could be induced to impact pathology in AD mouse models by exposing them to visual stimuli flickering on and off at 40 Hz. However, the effects lasted less than 24 hours and were limited to the primary visual cortex. The team developed new protocols to apply this non-invasive sensory stimulation repeatedly over days and weeks, and for using repeating auditory stimuli, as well as concurrent visual and auditory stimuli. In addition to longer-lasting effects on amyloid and tau pathology, researchers found that chronic GENUS significantly reduces the progression of neurodegeneration. They also detail new effects by GENUS on microglia, astrocytes, and the vasculature. Further, they report reduced AD pathology not just in primary sensory cortex, but in hippocampus and other higher-order brain regions. Accordingly, they also observed improved cognition in AD mice with repeated GENUS sessions. A major challenge in developing novel therapeutics for AD lies in its multifaceted pathology. Thus, the data support a non-invasive approach to manipulate neural oscillations that has the potential to impact Alzheimer's-related pathology and disease progression by multi-level intervention across the major brain cell types. The lab recently published two papers in this area (Adaikkan, C. et al., *Neuron*, 2019 and Martorell, A.J. et al., *Cell*, 2019.)

- Profiling the human brain in aging and Alzheimer's disease at single-cell resolution: A major challenge in developing novel AD therapeutics lies in its multifaceted pathology that impacts all the major cell types in the brain. The lab is applying massively parallel single-nucleus RNA sequencing in a comprehensive analysis of the transcriptomic changes in thousands of individual cells isolated from AD brains and control aged subjects. Previous studies in the field typically used tissue samples processed in bulk, where the majority of changes in gene expression can be attributable to only a few cell types. Additionally, more nuanced patterns of gene expression changes, which can differ between cell types, are generally masked. Researchers isolated, profiled, and analyzed single-nucleus transcriptomes from more than 80,000 cells. They were able to identify all the major cell types in the brain, differentiating between excitatory neurons and inhibitory neurons, as well as non-neuronal cell types

such as microglia, astrocytes, oligodendrocytes and oligodendrocyte progenitor cells. They identified more than 1,000 unique genes that change expression with AD pathology, implicating all major cell types. Specifically, they observed changes in the expression of multiple different genes with AD across different cell types that are involved in myelination (the process of creating a wrapping around nerve cell axons to allow them to communicate at high speed). They also found that the brain cells of men and women vary significantly in how their genes respond to the disease. Their work reveals unique cellular phenotypes as well as complex combinatorial effects in mixed cell populations that will need to be taken into consideration when designing therapeutic interventions. The lab recently published a new paper in this area (Mathys, H. et al., *Nature*, 2019).

Personnel

More than 337 community members participated in Picower Institute activities during the reporting period: 15 faculty members, four visiting scientists or scholars, 66 postdoctoral fellows, 28 research scientists, 60 undergraduate students, 54 graduate students, 52 research and technical staff, 18 administrative and service staff, and 40 research affiliates.

- In October 2018, Abby Reynolds was hired as program administrator, Silvia Darosa was hired as financial coordinator, and Katherine Olson was hired as administrative assistant II to Professors Flavell and Heiman.
- Dr. Emily Niederst was hired as director of scientific initiatives for the Aging Brain Initiative and Alana Down Syndrome Center in March 2019.
- Aimee Schroeder was hired as senior administrative assistant to Professor Tonegawa in April 2019.
- Kathleen Fitzgerald was hired as senior administrative assistant to Professor Tsai in May 2019.
- Lorena Pantano was hired as lead bioinformatician in April 2019, replacing Fan Gao.
- The laboratory of Mark Hyman Jr CD Associate Professor Gloria Choi transitioned to the Picower Institute from the McGovern Institute on January 1, 2019.
- The laboratory of Weifeng Xu closed on June 30, 2019. Xu did not receive tenure.
- The laboratory of Kay Tye closes on August 31, 2019. Tye has left MIT to join the Salk Institute.

Resource Development

The impressive success the Picower Institute has enjoyed over recent years continued in FY2019. These successes reflect the confidence of MIT's most generous alumni and friends, along with numerous corporations and foundations, in the Institute's ability to make valuable use of private resources. Picower resource development efforts identified and publicized more than 127 collaborative funding opportunities, extended print newsletter outreach to 2,702 individuals world-wide, hosted personalized visits with

more than 60 prospective and current donors, and helped host eight major development events on and off campus to extend visibility and relationships with a larger audience. With support from its communications director, the Picower Institute worked closely with its faculty to draft nine prize nominations and 35 new formal philanthropic proposals. Outright gift payments to the Institute for FY2019 totaled more than $19 million, and new philanthropic gifts and pledges totaled more than $30.6 million.

With the generous support provided from Barbara Picower, the JPB Foundation, and the late Jeffry Picower, researchers continued their ambitious research efforts and ventures into groundbreaking and transformational areas of neuroscience in pursuit of cures for brain illnesses. A new JPB gift commitment, totaling $750,000, will support researchers including new junior faculty member Choi in the Junior Faculty Development Program (JFDP). The JFDP provides mentoring and career development support to junior faculty at the Institute with particular focus on their 5th through 7th years at MIT, a critical time for progression to tenure. In FY2019, a total of $6.65 million in outright gift payments from the JPB Foundation continued to support major research programs at Picower Institute and two individual lab awards. These include the Picower Institute Innovation Fund (PIIF), the Picower Fellows Program, the Catalyst Program, a Junior Faculty Award for Flavell, and support for Tonegawa's laboratory. The PIIF is the institute's flagship program to empower its talented scientists to take risks as they conduct research into the greatest challenges and fundamental mysteries of neuroscience. To date, the PIIF has leveraged in more than $61.9 million in additional grant funding to the Picower Institute, generated more than 193 publications, launched three companies and has been the basis for global collaboration, firmly establishing the Picower Institute as a preeminent institute for neuroscience. The Picower Fellows program formalized a trainee structure to support the recruitment and retention of postdoctoral scientists. To date, this program has supported 38 individuals, including 26 international scholars, 14 female scientists, and two underrepresented minorities. The Picower Institute "Catalyst" Program (PICP) is a gift matching fund that leverages donations to jump start research partnerships with private sponsors. To date, each dollar donated to the Catalyst program has resulted in an additional $16.92 of vital research support, totaling $7.36 million in additional funding to the Picower Institute. JPB support has allowed researchers to achieve breakthroughs in 3D mapping of the brain, in understanding how synapses encode the learned information, and in identifying brain circuits and cellular 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.

As part of MIT's continued mission to help build a better world, the Picower Institute announced on March 20, 2019 the creation of the Alana Down Syndrome Center, an innovative new research endeavor, technology development initiative, and fellowship program launched with a $28.6 million gift from Alana Foundation, a nonprofit organization started by Ana Lucia Villela of São Paulo, Brazil. This new commitment builds upon a first gift to the Picower Institute (in 2015) of $1.7 million. The Alana Down Syndrome Center now builds upon that partnership to engage in a multidisciplinary research effort across neuroscience, biology, engineering, and computer science labs to increase understanding of the biology and neuroscience of Down syndrome. The center will also provide new training and educational opportunities for early career scientists and students to become involved in Down syndrome research and a four-year program with MIT's Deshpande Center for Technological Innovation in which creative minds

around MIT will be encouraged and supported in designing and developing technologies that can improve life for people with different intellectual abilities or other challenges.

Ana Lucia Villela attended the launch event along with her husband and two children as well as other family, friends, and Alana Foundation staff members who joined a large crowd to look on as Ana Lucia and MIT President Rafael Reif signed the ceremonial document establishing the center. The event also featured presentations from Alana co-directors Professor Angelika Amon and Professor Tsai, in addition to core collaborators Professors Ed Boyden, Manolis Kellis, and Mr. Leon Sandler—as well as senior Alana fellow Dr. Hiruy Meharena of the Tsai lab.

Significant efforts and development resources have continued to be directed toward a major cross-institutional health research initiative on brain aging and related cognitive decline, called the Aging Brain Initiative (ABI) at MIT. This initiative is led by Tsai along with seven founding faculty members from different disciplines across MIT and Michael Sipser, the dean of the School of Science. 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:

- a dinner hosted by MIT Corporation member Mark Gorenberg at his home in Palo Alto on September 17, 2018 for 23 MIT alumni, friends, and unaffiliated guests;
- an "insiders' update" event April 30th, 2019 for 12 VIP guests with presentations from eight ABI faculty and researchers hosted by MIT Chairman Robert Millard at the Picower Institute; and
- a dinner in NYC on June 13th, 2019 at Millard's home for 29 special guests, featuring Tsai.

All three events connected the institute's efforts with several influential unaffiliated individuals from around the world, many of whom have since visited campus, plan to visit this fall to see the work first-hand, or have given first gifts to MIT to support the research. The ABI also sponsored a new dinner event and weekend long symposium on May 3–5, 2019 with the BrainMind ecosystem—a platform and private community of top brain scientists, entrepreneurs, investors, philanthropists, and academic institutions collaborating to accelerate impactful innovation in brain science.

Notable new commitments in support of the ABI include a generous $800,000 pledge from Gary and Vicki Hua and a new $500,000 gift from Jeffrey Halis '76 and Nancy Halis. Both gifts support research to effectively translate the Institute's non-invasive GENUS research into human use. Similarly, new six-figure gift payments and pledges from the Robert A. and Renee E. Belfer Family, the Eleanor Schwartz Charitable Foundation, Elizabeth Kernan Siegelman SM '84, Russell Lewis Siegelman '84, Lester Gimpelson '57, and the Ludwig Family Foundation provided an additional $1.7 million in funds to support research and human studies for AD. The Belfer family also continued support for other breakthrough AD research at the institute through the Belfer Neurodegeneration Consortium (NDC), a collaborative enterprise comprised of renowned 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 of new ways to slow, stop, or reverse the progression of Alzheimer's with the goal of identifying and developing new therapeutic targets.

The Picower Institute helped to host our department's biannual, day-long Brains on Brains symposium to honor major donors and friends of our department and institute and to welcome new friends. The event took place on April 29, 2019 and featured inspirational talks, panel discussions on hot topics, and laboratory tours of new technology innovations from the institute. The event was exceptionally well-attended (approximately 200 registrants) and the day concluded with an intimate VIP dinner at Catalyst Restaurant, hosted by the Brain and Cognitive Sciences department head, Jim DiCarlo.

Additionally, this year the Picower Institute received generous five-figure and smaller annual fund gifts from MIT alumni and new unaffiliated donors, all of which have proved and continue to prove vital to Picower's mission of advancing brain research.

Media Recognition

The Picower Institute has attained a distinguished international reputation as a leader in neuroscience research. The scholarly excellence of the faculty is reflected in their distinguished publication records. In the reporting year, Picower Institute faculty published 64 articles, with publications in hallmark journals such as *Nature, Cell, Neuron, Cell Reports, Nature Neuroscience,* and *Nature Communications*.

During this reporting period, the Picower Institute posted 16 feature stories on its website and social media feeds and 26 press releases, often working with the MIT News Office. Picower research and commentary was reported more than 100 times by news sources including *The New York Times*, National Public Radio, *The Los Angeles Times*, *The Boston Globe*, *Popular Science*, *The Atlantic*, *Scientific American*, *The Scientist*, *Nature*, *STAT*, *New Scientist*, *BuzzFeed*, and *Psychology Today*.

Programs and Activities

Collaboration among disciplines is an integral component of the Picower Institute's research philosophy. To facilitate collaboration, the Picower Institute plans a rigorous calendar of formal lectures, conferences, and workshops, as well as other informal events. Activities 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 offer to science and society.

The Picower Institute Colloquia bring the highest caliber of 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 were: Dr. Matthew Chafee of the University of Minnesota, Dr. Sara Aton of the University of Michigan, Dr. Scott Waddell of the University of Oxford, Dr. Huizhong Tao of the University of Southern California, and Dr. Marcy MacDonald of Harvard Medical School and Massachusetts General Hospital (MGH).

In neuroscience, "plasticity" refers to the crucial physical changes 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 postdocs and graduate students from across the institute a chance to share their latest, often pre-published, research with colleagues within the Building 46 community. The series provides an opportunity for participants to improve their presentation skills and fosters collaborations and builds new relationships across disciplines and between laboratories.

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

The Picower Institute hosted the annual fall symposium, "Frontiers in Neurotechnology," on October 23, 2018. Experts from around the globe gathered to share their latest research findings relating to the development and application of state-of-the-art technologies to unlock the mysteries of the brain. The event was well-attended with about 450 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 work of a current leader in the area of brain research. This year's lecturer on April 23, 2019, was Dr. Karel Svoboda of HHMI's Janelia Research Campus (in Ashburn, Virginia).

Together with the School of Science, the Picower Institute continued the recently launched Aging Brain Seminar Series, a seminar series focused on fundamental and translational aging brain research. This series is part of the growing ABI and has the goal of bringing together bright minds to give talks that are idea-focused, and on a wide range of brain-aging subjects to foster learning, inspiration, and wonder—and provoke conversations that matter. Aging Brain speakers included: Dr. Magdalena Götz of the Ludwig Maximilian University of Munich and Dr. Michael Heneka of the German Center for Neurodegenerative Disease.

There were also several special seminars held during the academic year. Speakers included: Dr. Hiroki Ueda of the University of Tokyo and RIKEN Quantitative Biology Center, Dr. Laura Colgin of the University of Texas at Austin, and Dr. Kazuo Tsubota of Keio University.

After the close of the academic year, the Picower Institute hosts an annual retreat for its community members. More than 160 Picower Institute members attended this year's retreat held June 3-4, 2019 in South Yarmouth, MA at the Red Jacket Beach Resort. The retreat included 10 speakers as well as 28 poster presentations as well as a keynote address by Dr. Gordon Fishell of Harvard Medical School. A delegation of five scientists from the RIKEN Brain Science Institute also attended the retreat and toured Picower labs afterward.

An endeavor targeted to the Picower Institute's postdoctoral community provided resources to support activities that build community and enrich interactions between postdoctoral colleagues and future associates. The Postdoc Association, now a Building 46-wide association, continues to expand and make improvements in partnership with administration for the postdoc community. Throughout the past year the postdocs 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 a truly unique research environment with support for Picower Institute faculty, lab members, and administrative team. The programs include: (1) The Clinical Collaborative Fellowship, (2) The Picower Neurological Disorder Research Fund, (3) Picower Fellows Program, (4) The Symposium Fund, (5) The Picower Institute Innovation Fund, (6) the RIKEN-MIT Center for Neural Circuit Genetics, and (7) The Catalyst Program.

Research Initiatives

RIKEN-MIT Laboratory for Neural Circuit Genetics

Established in April 2008, the RIKEN-MIT Laboratory for Neural Circuit Genetics is directed by Susumu Tonegawa and jointly sponsored by the RIKEN Center for Brain Science in Japan and MIT. The laboratory's objective is to deepen our understanding of molecular, cellular, circuits, and brain systems mechanisms underlying learning and memory 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. This research is important for uncovering the fundamental mechanisms operating in the healthy brain and for understanding how these mechanisms go astray under disease conditions. The RIKEN-MIT agreement funds the activities of the laboratory, and will primarily support the Tonegawa research group for the next four years (as of April 2019). In the past year, there were two Tonegawa Lab publications partially funded by this collaboration: Tonegawa, S. et al., *Nature Reviews Neuroscience*, 2018, and Pignatelli, M. et al., *Neuron*, 2019.

iPS Core Facility

Picower launched the iPS Core Facility (ICF) in November 2010. It integrates the various research goals of members of the Picower and McGovern Institutes and the Department of Brain and Cognitive Sciences to create human and animal cell models of diseases. The various laboratories have expertise and experience with different experimental protocols which, when combined in a collaborative manner with 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, and opened its doors for the first time 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 (iN) cells, and neural organoids. The ICF has approximately 1,600 square feet of space in three tissue culture areas; one room is dedicated for viral work with iPS ES cells as BL2plus practice for higher safety protocol, and two tissue culture areas are for maintenance, expansion,

and general handling of non-viral work related iPS and ES cell culture with BL2 safety practice. There are 14 bio-safety cabinets, 24 CO2 incubators including three of three -gas incubator that allows controlling of hypo- or hyper-O2 concentration, and bench areas. There are also four bio-safety 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 disease, Down syndrome, and from healthy people. Isogenic iPSC lines are also generated and used for various disease model research in Alzheimer's and Down syndrome.

ICF supervisor Tak Ko has also set up an orientation program and trainings to educate faculty and potential users. The ICF provides a powerful incentive for different labs to collaborate and exchange ideas. Since its inception, the facility has been used by more than 25 researchers at MIT. Moreover, collaborations with researchers outside MIT have been continuing with noteworthy interactions with the Broad Institute and biotech industries. Many prominent articles have been published and accepted in various journals including *Nature, Neuroscience, PLoS One*, and *Molecular Psychiatry* based on data using the ICF.

MIT researchers have leveraged ICF capabilities to receive external funding on numerous occasions. Projects included: "The Alzheimer's Disease Risk Genes in Human Microglia and Neurons Derived from iPSCs" and "Chemical Genomic Approaches to Neurobiology of DISC1," as well as research on the cdk5/p35 kinase.

Bioinformatics Core Facility

The Picower Institute bioinformatics core facility was established in March 2012 to provide computational support to Picower investigators. The vision is to support the experimental design of studies, develop novel computational pipelines that fit the institute research, and offer teaching material and personal support to disseminate our knowledge to scientists during their research. The facility focuses on the analysis of high-throughput data, primarily, sequencing data, such as ChIP-seq, bulk-RNA-seq, Single-Cell-RNAseq, and small RNA-seq. In 2019, the facility joined the McGovern cluster (OpenMind) allowing it to escalate accordingly to the amount of data it acquires and the volume of experiments that increase exponentially every year. The facility contributes and supports open-source community code and isolated environments to the researchers to boost the efficiency and reproducibility of the analysis. All courses and pipelines are published on GitHub and there is an operating protocol using MIT GitHub to manage different projects from each laboratory—allowing for transparent communication of results and analysis. Moreover, a knowledge base site helps to collect protocols, tutorials, and resources. It shows the current load of the core and it has a private space only available to MIT researchers. The facility will continue focusing on adapting analysis to the best practices, developing new materials for teaching, and collaborating openly with Picower researchers.

CLARITY Core Facility

In 2015, the Picower Institute created a shared CLARITY imaging core equipment facility to allow it to lead brain mapping microscopy methods to strategically make new advances and delve into unexplored areas of neuroscience research. The facility includes

hardware and software infrastructure for 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, especially by the Chung, Sur, Tsai, Tye, Nedivi, Tonegawa, and Xu labs, however the equipment is available to all Picower labs and is available for use 24 hours per day, seven days a week. Videos and data collected using this new technology are used in published research, and shown at conferences. Particularly notable are videos depicting clarified mouse and human patient post-mortem brains showing new pathological information for diseases such as Alzheimer's.

The Aging Brain Initiative

As described in "Resource Development," the ABI continues to have senior leadership support within MIT's Campaign for a Better World. The bold goals of this program 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 aims to bring MIT's leading memory and neurobiology researchers together with experts from other disciplines—including engineers, computer scientists, economists, urban planners, and social policy experts—into a single cohesive group with clinicians and industry partners to think creatively about brain aging and to collectively tackle ambitious ideas that have not otherwise been pursued. 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 to include vital aspects of the challenge—such as understanding memory loss and developing technologies for improved study and care. Frequent multi-disciplinary discussion forums and bi-monthly seminars enable open sharing of data and accelerated pollination of ideas for growth into new areas.

In addition to several major events to raise awareness and increase the visibility of the effort this past fiscal year, ABI director Tsai was invited to give a talk about the initiative's work to the MIT Presidential CEO Advisory Board meeting in June 2019 and to participate in the Nobel Prize Dialogue conference on The Future of Ageing (hosted in partnership with the Fundación Ramón Areces) in Madrid on May 22, 2019.

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, aide home care and point toward a cure for diseases like dementia. Flagship projects currently center around MIT strengths such as (1) Big Data -omics approaches to understanding brain aging and disease, (2) Circuit and systems designed therapeutic approaches including non-invasive stimulation regimens and ways to restore memories, (3) Personalized approaches to treatment through human and new models of disease, and (4) Uncovering the secrets to healthy aging and resilience.

In FY2019, members of the team published new breakthrough discoveries and major advancements including a Cell and Neuron paper on advancements on our potential non-invasive light and sound GENUS therapy for Alzheimer's disease. In May, Li-Huei Tsai and Manolis Kellis revealed a new comprehensive single-cell map of how Alzheimer's

affects the brain in *Nature* (and tweeted by Bill Gates). Myriam Heiman discovered a new hallmark of aging in neurons and Elly Nedivi's team found that Prozac restores flexibility in aging neurons. This past fiscal year, the group has continued exciting translational work on non-invasive methods for treating AD and have completed early safety, compliance, and feasibility studies in healthy human volunteers and are beginning testing in patients. Preliminary results suggest the approach is both safe and feasible.

Faculty Research Summaries

Picower Institute faculty research areas are summarized below:

Mark Bear

Mark Bear is a Picower Professor of Neurosciencein BCS. His research topic is "How is the brain modified by experience, deprivation, and disease?"

The overarching interest of this research 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. It sculpts connections during postnatal development to determine the capabilities and limitations of brain functions, and is responsible for the reorganization of the brain after damage. It is vulnerable in numerous psychiatric and neurological diseases and contributes to their symptoms.

Historically, 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 (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, the Bear Lab 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, the lab 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, the lab discovered that protein synthesis (and LTD) downstream of mGluR5 is exaggerated in the mouse model of fragile X (FX). Human FX 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: (1) mechanisms and regulation of naturally occurring synaptic plasticity in visual cortex; (2) pathophysiology and treatment of genetically defined developmental brain disorders (particularly fragile X); and (3) using knowledge of synaptic plasticity to promote recovery from amblyopia. The lab primarily studies mouse models, and using a broad range of methods that include, but are not limited to, brain slice electrophysiology and biochemistry, in vivo electrophysiology and 2-photon functional and structural imaging, and behavioral analysis. The lab is "question-oriented" rather than "method-oriented," applying any technology that is needed to address the questions of greatest interest.

Emery Brown

Emery Brown is the Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience in the Institute for Medical Engineering and Sciences (IMES) and BCS. His research areas are "Neural Signal Processing Algorithms" and "Understanding General Anesthesia."

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 developing statistical methods and signal-processing algorithms for neuroscience data analysis. The lab has used its 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 fMR imaging time-series
- construct algorithms for neural prosthetic control 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
- track brain states under general anesthesia

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 US for more than 165 years and currently more than 100,000 US people receive general anesthesia daily for surgery alone. Still, the mechanism by which an anesthetic drug induces general anesthesia remains a medical mystery. The lab uses a systems neuroscience approach to study how the state of general anesthesia is induced and maintained. To do so, the lab is using fMRI, EEG, neurophysiological recordings, microdialysis methods, and mathematical modeling in interdisciplinary collaborations with investigators in the Harvard-MIT Program in Health Sciences and Technology (HST), BCS, MGH, and Boston University. The long-term goal of this research is to establish a neurophysiological definition of anesthesia, 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 in BCS.

The primary goal of Choi's research program is to elucidate the mechanisms through which the immune system modulates neural circuit function, ultimately shaping animal behavior. Choi and other researchers 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 the Choi Lab has shown to require the activity of maternal T helper 17 (Th17) cells and the cytokine interleukin (IL)-17a they secrete. Research 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^{+} (PV^{+}) 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 Neurosciencein BCSs, the Department of Chemical Engineering, and IMES.

Chung is leading an interdisciplinary research team devoted to developing and applying novel technologies for holistic understanding of large-scale complex biological systems. In the past year, his group has continued to develop new technologies, such as SHIELD, to accelerate the pace of scientific discovery and development of therapeutic strategies in a broad range of biomedical research. The Chung lab has openly shared the SHIELD reagents and protocols with more than 100 labs worldwide. His group has active collaborations with many researchers at MIT, Broad Institute, MGH, and Harvard. He has traveled extensively including University of Washington, Stanford University, ETH Zurich, University of Laval, as well as Cold Harbor Asia, to speak about his group's technologies and their applications. Chung taught 10.302 Transport Processes and HST.562 Pioneering Technologies for Interrogating Complex Biological Systems. He also served on the IMES Committee for Academic Programs, as well as the Chemical Engineering graduate admission and BCS graduate admission committees. Chung recently founded a start-up, LifeCanvas Technologies, which aims to advance the adoption and usage of Chung Lab technologies developed at MIT.

Steven Flavell

Steven Flavell is the Lister Brothers Career Development Assistant Professor in BCS.

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, researchers

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, like 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 (Flavell et al., *Cell,* 2013). This work demonstrated 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 acid-sensing ion channels (ASICs) mediate the detection of gut bacteria is particularly exciting and the subject of a new line of studies in the Flavell Lab.

Work in Flavell's lab continues to ask fundamental questions about how behavioral states are generated and how environmental cues influence state generation:

- What circuit-wide patterns of activity define the stable configurations for different behavioral states? How are these patterns stabilized by neuromodulators like serotonin? Towards this end, his lab constructed a microscope that is suitable for whole-brain calcium imaging and has used this new technology to characterize large-scale neural activity patterns associated with distinct behavioral states (manuscript in preparation).
- 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.
- The Flavell Lab has also expanded their studies to more broadly examine how animals coordinately alter many ongoing behaviors as they switch between behavioral states. They built a set of microscopes that can record C. elegans animals for their entire lifespans and developed machine vision software to automatically quantify every behavior generated by each animal. This imaging platform revealed a new role for dopamine in coupling premotor circuits as animals switch behavioral states. Interestingly, dopamine acts via both D1- and D2-type receptors to coordinate premotor circuits, similar to its function in the mammalian striatum (manuscript in preparation).
- 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 in BCS and a 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 the lab views 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.

Researchers 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 have revealed that mitochondrial function is perturbed early on in the most vulnerable cell types in HD. Using this knowledge, the lab is currently testing and designing strategies to increase mitochondrial function to see if doing so can halt the progression of HD symptoms in mice.

In a separate line of research, using a genome-wide, unbiased in vivo shRNA and now CRISPR genetic screening methodology, in the past few years the lab has identified a number of genes essential for neuronal viability in vivo, both in pathways previously implicated in HD, as well as several novel targets. This past year the researchers have focused on a new gene target that has emerged from these screens, which are believed to contribute to mitochondrial homeostasis. Researchers are actively pursuing genetic and small molecule means to boost this gene's function in the brain.

Finally, the lab has recently begun profiling gene expression changes in human post-mortem HD tissue, to validate results from our mouse model studies at the cell type-specific level. Additionally, in the last few years the researchers have performed extensive molecular profiling of neuronal subtypes under chronic administration of both typical and atypical antipsychotic drugs that are used to treat schizophrenia. Their studies have suggested the 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 new collaborative study with NIH researchers the lab is testing whether antipsychotic drug treatment can modulate resilience to compulsive drug use.

Moving forward, the researchers have started two new projects in the lab aimed at: (1) profiling the molecular characteristics of cells that comprise the human blood-brain-barrier, as these cell types have been implicated in many neurodegenerative diseases including HD; and (2) studying the cell type-specific effects of cannabis on the developmental, adult, and degenerating brain.

Troy Littleton

Troy Littleton is a Menicon Picower Professor of Neuroscience in BCS and Biology.

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. The lab uses the Drosophila model to study how these basic synaptic mechanisms are dysfunctional in several neurological disorders, including epilepsy, Huntington's disease and autism.

Earl Miller

Earl Miller is a Picower Professor of Neuroscience in BCS.

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—which 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 non-human primates are so adept.

Elly Nedivi

Elly Nedivi is the William R. (1964) & Linda R. Young Professor of Neuroscience in BCS 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), the lab has 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. The 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, the Nedivi Lab 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 the Paul E. Newton Professor of Neuroscience in BCS and the 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 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 the Sur Lab is to understand long-term plasticity and short-term dynamics in circuits of the developing and adult cortex, and to utilize this understanding to discover mechanisms underlying disorders of brain development.

Susumu Tonegawa

Susumu Tonegawa is a Picower Professor of Neuroscience in BCS and Biology.

This lab continues to focus on the molecular, cellular, and systems neuroscience of learning and memory. At the heart of memory research is the question of 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. The lab has 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 ("engram"). 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, the lab continues to elucidate engram mechanisms for various types of memory (such as emotional and social), including consolidation and retrieval. The lab is also evaluating applications of such knowledge that could facilitate the amelioration of human brain disorders such as Alzheimer's disease. Currently, the lab is focused specifically on several important topics that are critical for better a understanding of memory in the mammalian brain:

- What is the role of engram excitability in memory retrieval?
- Characterizing the role/mechanism for prefrontal cortex (mPFC) engrams in memory consolidation;
- Determining the role of hippocampal vCA1 neurons in memory disorders such as Alzheimer's;
- Elucidating the role of the basolateral amygdala in fear extinction; and
- Exploring the use of "chunk code" to organize episodic memory.

The Tonegawa Lab currently has two papers on the topics of fear extinction and chunk code under review for publication in major journals.

Li-Huei Tsai

Li-Huei Tsai is a Picower Professor of Neuroscience in BCS.

The Tsai Lab is interested in elucidating the pathogenic mechanisms underlying neurological disorders that impact learning and memory. The lab is taking a multidisciplinary approach to investigate the molecular, cellular, and circuit basis of neurodegenerative disorders.

The lab's three main approaches are:

Transcriptomic and epigenomic analysis of brain disorders

The Tsai Lab is 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, the lab is 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 30-80 Hz) are associated with higher order brain functions, and may be disrupted in the early stages of AD in human patients as well as in mouse models. The researchers are thus interested in applying circuit manipulations to ameliorate cognitive deficits in AD. Through the targeted application of optogenetic and chemogenetic tools, the lab also aims to manipulate the activity of specific neural populations and circuits to gain insights at the intersection of pathology, network activity, and behavior. Additionally, the lab is mapping out the sequential temporal and spatial disruptions of neural circuits by the deposition of amyloid and aggregated tau protein in AD, to identify nodes of vulnerability and to understand how these pathologies propagate throughout the brain.

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

The lab has generated numerous iPSC lines by reprogramming fibroblasts from healthy individuals, as well as from late onset sporadic Alzheimer's disease (LOAD), early onset familial AD (fAD), and Down syndrome patients. To assess the phenotypic consequences of disease-associated genetic variants, the lab additionally applies 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 non-coding genetic variants of AD 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, researchers can recapitulate and study complex in vitro models of human brain tissue.

Matthew Wilson

Matthew Wilson is a Sherman Fairchild Professor in Neurobiology in BCS and Biology.

Work in Matthew 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, providing the means to establish the 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 have identified novel circuits involved in the regulation of attention and sleep, and demonstrated the role of brain rhythms in enhancing memory performance.

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