Department of Brain and Cognitive Sciences

Mission

The mission of the Department of Brain and Cognitive Sciences (BCBS) is to understand how the brain gives rise to the mind. We are a department with a unique vision anchored in the idea that a deep understanding of the mind requires the synergy of multiple levels of analysis: characterization and investigation of human cognitive phenomena in both normal and disordered states; the neuronal circuits, algorithms, and representations in the brain that underlie those phenomena; and the cellular, molecular, and genetic mechanisms that develop, implement, and maintain those circuits. We believe that building links among these levels—links often specified in the language of engineering—is the key to understanding how the brain gives rise to the mind. We also believe that this deep understanding is the key to solving disorders of the mind, building truly intelligent machines, and advancing education, among myriad other unpredictable world-changing impacts.

Because the path from mechanistic, basic science to translation is both critical and unpredictable, BCS aims to offer an environment in which the world's most talented researchers can pursue new ideas about the underlying mechanisms of the brain and then collaborate when larger groups are needed and/or translational connections are visible. We also uphold a core value of MIT: that sufficient explanations of these processes must ultimately be rooted in the language of mathematics and computational theory.

A unique and defining identity of our department is that we pursue all of these levels of analysis in an integrated and synergistic way. There are very few other departments in the world organized in the same manner as BCS—in most universities, the study of the brain (neuroscience) and the study of the mind (cognitive science) are housed in separate buildings, and often on separate campuses. At MIT, the Brain and Cognitive Sciences Complex, also known as Building 46, houses the McGovern Institute for Brain Research (MIBR) and the Picower Institute for Learning and Memory (PILM) as well as the department. The mission of BCS thus spans research, teaching, and training in both neuroscience and cognitive science.

Leadership

The department plays an important "umbrella" role in building and strengthening the brain and cognitive science community at MIT. Our overall strategy, which focuses on bolstering the subcommunities that naturally cross cut the entirety of Building 46, has helped to lower the walls between the various units and created opportunities for the community to come together.

Building-wide leadership: The BCS Council includes Jim DiCarlo, BCS department head (chair); Professor Bob Desimone, director of MIBR; Professor Li-Huei Tsai, director of PILM; Professor Mriganka Sur, director of the Simons Center for the Social Brain; Professor Tomaso Poggio, director of the Center for Brains, Minds, and Machines; and senior and junior faculty members spanning all areas of the department. The council

meets monthly and serves as an advisory committee to ensure that departmental decisions are strongly informed and that all leaders in the building are comfortable and enthusiastic about those decisions.

BCS faculty leadership roles: The department would not be able to plan and execute its myriad functions without the support of the faculty, and we continue to espouse a culture of shared effort. The following faculty have notably stepped up to continue and/or take on key leadership roles over the last four years:

- Professor Michale Fee (associate department head for education and chair of the BCS Education Committee)
- Professor Laura Schulz (undergraduate officer)
- Professor Matt Wilson (graduate officer and chair of the BCS Graduate Admissions Committee and BCS Graduate Affairs Committee)
- Professor Nancy Kanwisher (BCS space oversight)
- Associate Professor Alan Jasanoff (chair of the BCS Seminar Committee)
- Professor Pawan Sinha (chair of the BCS Diversity Committee)
- Professor Mark Bear (postdoctoral officer for the BCS community)

All primary BCS faculty actively serve on one or more of these standing committees.

Faculty

BCS faculty members are widely recognized as being among the leaders in their respective fields. Our faculty includes one Nobel Prize winner, nine members of the National Academy of Sciences (including two emeritus members), five members of the National Academy of Medicine, 18 members of the American Academy of Arts and Sciences (including two emeritus members), one National Medal of Science awardee, one winner of the Kavli Prize, seven winners of the Troland Award from the National Academy of Sciences, and four recipients of the Society for Neuroscience Young Investigator Award.

The McGovern Institute for Brain Research and the Picower Institute for Learning and Memory are critical components of the BCS community: 27 of the 36 BCS primary faculty are also investigators in the McGovern and Picower Institutes. All 14 of the PILM investigators have either their primary (11) or secondary (three) appointments in BCS, and 17 of the 18 MIBR investigators have their primary (14) or secondary (three) appointments in the department.

Two BCS faculty members have core appointments at the Broad Institute, two have joint appointments at the Institute for Medical Engineering and Science, and two hold the special title of Institute Professor. Two faculty members, Emeritus Professor Emilio Bizzi and Professor Gerald Schneider, marked the beginning of their retirements this year. We are appreciative of the contributions these esteemed faculty members have made to the department and wish them the best on their next chapter.

The interdisciplinary nature of neuroscience and cognitive science is highlighted by the number of BCS faculty with joint appointments. The faculty members who held joint appointments this past year in BCS represent Chemical Engineering, Mechanical Engineering, the Media Laboratory, Biology, Biological Engineering, the Sloan School of Management, and the Weizmann Institute of Science. BCS faculty members in turn hold secondary appointments in many of those departments, as well as in the Linguistics section of Linguistics and Philosophy.

The BCS community was saddened by the loss of Richard M. Held, a professor emeritus and former head of MIT's Department of Brain and Cognitive Sciences, who passed away in November 2016 at age 94. Held spent his career researching how the visual system develops and adapts, a topic he was very passionate about. Throughout his tenure at the helm of BCS from 1977 to 1986, Held mentored several generations of graduate students and oversaw the department's growth into one of the premiere neuroscience and cognitive science institutions. Even after his retirement he remained active in the BCS community, joining Professor Pawan Sinha's laboratory to become a collaborator in Project Prakash, a nonprofit founded by Sinha that seeks to restore the sight of congenitally blind children in India and research their subsequent development of vision. His profound impact on our community and on MIT's excellent reputation in the fields of neuroscience and cognitive sciences can still be felt today. He will be deeply missed.

Development

BCS continues to build momentum in its development activities. We have created a comprehensive resource development program that includes individual giving, planned giving, foundation and corporate support, donor communications, stewardship, and donor-centric events. The primary goal of the program is to increase philanthropic funds to support students, faculty, and, more broadly, fundamental neuroscience and cognitive science research.

During this time of economic uncertainty, philanthropic support will be a critical source of funding to advance the department's research and educational missions. The department's top fundraising priority continues to be increasing fellowship support for graduate students. This support is a vital component of our ability to attract the very best young scientists and is important in ensuring that BCS remains a leader in education and research. Our goal is to build an endowment capable of fully supporting our graduate students for a minimum of their first three years in the department. The Champions of Brain Fellows Society continues to be valuable in helping the department secure both endowed and expendable fellowship funding. We recently had success raising fellowships through a generous match opportunity; two gifts from two new donors to BCS were matched to the endowed level.

In addition to fellowship support, the department is deeply focused on increasing resources for research in the science of natural intelligence and its intersection with applications in artificial intelligence (AI) and cognitive computing. The issue of intelligence—how the brain produces intelligent behavior and how this can be replicated in machines—is one of the greatest challenges in modern science. This area of study is becoming increasingly important and relevant in today's society but is lagging in

research support at MIT. It is an opportune synergistic interaction between MIT science and engineering: transformative advances in AI will result from work aiming to describe the mechanisms of the human mind in engineering terms, and a tight coupling of computational model building with empirical brain and cognitive science is critical to understanding how the brain gives rise to the mind. To catalyze this global effort, we propose the creation of an endowed intelligence institute at MIT dedicated to the science and engineering of intelligence. We have been executing many activities and discussions in this space. For example, we have created fundraising materials and organized donor-centric events related to intelligence and cognitive computing research at BCS, and we have partnered with the Computer Science and Artificial Intelligence Laboratory to create a white paper outlining our vision for an intelligence institute.

Additional fundraising targets include establishing named research funds to support faculty projects, increasing funds for postdoctoral fellowships, and securing funds to support mechanisms for unrestricted research support and diversity initiatives in the department. Our comprehensive development program and events such as the Brains on Brains Symposium will help us continue to identify new donors and cultivate these relationships. Our May 2017 Brains on Brains Symposium is a testament to the importance of these events; more than $2 million in new pledges resulted from this year's symposium. In addition to organizing lab visits, tours, and meetings, BCS participated in more than 12 events over the past year, including panels, donor dinners, and fireside chats.

Education and Training

BCS provides its students with an interdisciplinary curriculum designed to educate them and prepare them to be future ambassadors of science. Our intensive undergraduate program is a tiered system that builds on the expertise gained at each preceding level. Beginning with broad courses, students gain foundational knowledge of topics drawn from molecular, cellular, and systems neuroscience; cognitive and perceptual psychology; applied mathematics; computer science and artificial intelligence; linguistics; and philosophy of mind. These multiple tiered pathways through the undergraduate program are designed to prepare students for a range of possible career paths, including research, health care, and industry. The graduate program provides advanced instruction on topics and research methods in one (or more) of four themes: molecular and cellular neuroscience, systems neuroscience, cognitive science, and computation. Our faculty taught a total of 53 subjects in our undergraduate and graduate curricula this past year.

Undergraduate Program

BCS, now in the fourth year of our undergraduate curriculum redesign, has provided our students with opportunities to build a strong quantitative skill set and be rigorously exposed to an engineering-level description of neurons and neural circuits and the computations they carry out. All undergraduates in BCS learn elementary computer programming and statistics and take the foundational course (9.40) that covers quantitative and computational approaches to understanding the brain and behavior.

Students in the department are often quite accomplished and recognized as such. In 2016–2017, two of our students were Burchard Scholars, two received Ronald E. McNair Scholarships, and one was a Schwarzman Scholar. Two students were finalists for the Rhodes Scholarship, Marshall Scholarship, and Truman Scholarship.

Institute awards presented to undergraduates include the Walle J.H. Nauta Award for Outstanding Research in Brain and Cognitive Sciences (six) and the BCS Hans Lukas Teuber Award for Outstanding Academics (16). Additionally, one of our undergraduates was the first student recipient of the MIT Collier Medal for outstanding service and selfless acts of kindness to the MIT community.

Over the past year, 25 students graduated with degrees in brain and cognitive sciences.

Graduate Program

The department has added a focus on improving professional development in the areas of presentation skills and paper critiquing. During the fall of 2017, Professor James DiCarlo successfully developed and taught Research Paper Dissection, a course taken by first-year graduate students. The course teaches students to distill and critically evaluate the key claims in a cutting-edge research paper and how to give an oral presentation while defending or critiquing those claims. Background material for each paper is provided. Papers span all areas of neuroscience and are chosen in line with each week's BCS departmental colloquium, given by a prominent visiting scientist. The goals of the course are to train new students in reading, reviewing, and presenting cutting-edge research; to give students background knowledge in disparate areas of neuroscience; and to build students' confidence in asking critical questions of scientists both in and outside their primary field.

Over the past five years, the size of our graduate program has remained steady at around 100 students (approximately 2.5 students per faculty member). Twenty-one graduate students entered in fall 2017. Forty-eight percent of these students were female, 20% were international students, 14% were underrepresented minority students, and 10% were classified as economically disadvantaged. Eleven of the incoming students were funded by Singleton Presidential Graduate Fellowships, one by a Garvey Fellowship, one by a Department of Energy computational fellowship, one by a CONACTY Fellowship (Mexico), and seven by National Institutes of Health (NIH) training grant programs.

Over the past year, 20 students graduated with doctorates: Idan Blank, Rebecca Canter, Matthew Dobbin, Omar Durak, Danielle Feldman, Richard Futrell, Lea Hachigian, Bryan Higashikubo, Hannah Iaccarino, Kean Jaime Bustamante, Shaiyan Keshvari, Simon Kornblith, Tejas Kulkarni, James Mutch, Gerald Pho, Rajeev Rikhye, Dheeraj Roy, David Scott, Jakob Voigts, and Sangyu Xu.

BCS graduate students are also highly accomplished. One student received a National Science Foundation Graduate Research Fellowship, one received a Legatum Center Fellowship, and one received an MIT Office of Graduate Education Whitaker Health Sciences Fund Fellowship. Institute awards over the past year include the Angus MacDonald Award for Excellence in Undergraduate Teaching (seven), the Walle Nauta Award for Continuing Dedication to Teaching (two), the Walle Nauta Award for Excellence in Graduate Teaching (two), the Harold M. Weintraub Graduate Student Award (one), and the Graduate Women of Excellence Award (one).

Postdoctoral Program

The directors of BCS, MIBR, and PILM deeply believe in creating and maintaining an environment where postdocs can learn by doing unfettered science to achieve their career goals. To this end, we have worked to reduce stresses that interfere with scientific inquiry. A major stress, particularly in the Boston area, is the cost of living. Therefore, over the past year we have worked on developing and executing a plan to improve the annual stipends that postdocs receive here as scientists in training.

As of July 1, 2016, we raised the postdoc minimum annual stipend rate for the BCS community (BCS, MIBR, and PILM) to a level significantly above the current NIH Kirschstein National Research Service Award minimum and in line with the level recommended in a recent National Academy of Sciences study of postdoctoral salaries (approximately $50,000). The new minimum stipend is indexed to the NIH year 4 rate (currently $51,120). This minimum stipend level is guaranteed for each of the four to five years of the postdoctoral period and is adjusted for cost of living when the NIH scale is adjusted. The new annual stipend policy applies to both postdoctoral fellows and postdoctoral associates. This year we successfully implemented the policy to resounding positive feedback from our community, postdocs and faculty alike.

Another source of stress for postdocs is career anxiety. Thus, BCS postdoctoral officer Mark Bear spearheaded an initiative to gather data on training outcomes for postdocs matriculating in the past decade. The initial results were quite encouraging, with two thirds of our postdoctoral alumni moving directly from MIT into faculty positions and science-intensive positions, including the pharmaceutical industry. In an effort to understand how our outcomes compare with peer institutions or national averages, we reached out to the National Academy of Sciences. We were surprised to learn that we are leading the way in collecting such data, so no reliable comparisons are available. Nevertheless, we did find that the outcomes of the postdoctoral experience exceed expectations and allay the fears of our current postdocs.

Selected Research Highlights

Edward Adelson

Adelson's laboratory studies various problems in perception from a psychophysical and computational viewpoint. Human vision, computer vision, and computer graphics have traditionally been the center of the group's research, but recently they have incorporated artificial touch perception as well. They are building soft and sensitive touch sensors for robotic fingertips, based on an elastomeric technology called GelSight, and applying them to artificial manipulation and surface sensing. Additionally, the lab works on artificial touch sensors for robotic touch and manipulation. The sensors developed by the group have the softness of human skin and extremely high resolution, delivering rich information about force, shear, shape, and texture. The spatio-temporal signal is high-dimensional, and they are now using machine learning to convert the raw signal to meaningful inferences. They have successfully estimated the hardnesses of touched objects of unknown geometry, which is completely beyond the capabilities of any previous sensor. The lab has also been successful in recognizing the tactile properties of fabrics and correlating a fabric's visual appearance with its tactile qualities.

Mark Bear

The central question addressed by the Bear laboratory is how sensory experience and deprivation modify the brain. The group's current focus is on exploiting their knowledge of the elementary mechanisms of synaptic plasticity to overcome genetic or environmental adversity. This interest is pursued in the context of recovery from the effects of monocular deprivation in early life and recovery from the effects of gene mutations that are associated with psychiatric illnesses characterized by cognitive impairment. Ongoing studies are (1) exploring the limits of adult recovery from visual deprivation and testing specific hypotheses for improving the prognosis based on the principles of synaptic plasticity, (2) examining the synaptic basis for visual recognition memory and how this is affected by gene mutations that impair cognition, and (3) testing the hypothesis that several genetic mutations that cause autism and intellectual disability converge on a common synaptic pathophysiology involving the regulation of protein synthesis by glutamate receptors. Perhaps the most exciting discovery out of the Bear lab in the past year was the finding that visual impairment can be reversed in animal models of amblyopia by "rebooting" the visual system. Amblyopia, the most common form of visual disability in children, is a consequence of an imbalance in the inputs to the brain from the two eyes. It is modeled in animals by temporarily depriving one eye of vision. A lasting consequence of monocular deprivation is a loss of responsiveness of brain neurons to stimulation of the deprived eye. The lab's work suggested the possibility of rejuvenating weak synapses by briefly blocking all activity in both eyes with a local anesthetic. Remarkably, this procedure worked—in two species, they showed that vision fully recovers in the formerly deprived eye following retinal inactivation. They are now working to understand the mechanisms behind this recovery and hoping to apply these insights to develop novel treatments for human amblyopia.

Emilio Bizzi

One of the central questions in the field of motor control is how our motor goals are translated into actions. The Bizzi laboratory has elaborated a theoretical and experimental framework that describes the way in which the central nervous system (CNS) transforms planned movements into muscle activations. Among the techniques used by the lab are behavioral training, cortical recording from single neurons, electromyographic (EMG) recording of muscle activity, microstimulation, cellular inactivation, kinematic measurement of movements in three dimensions, functional imaging, and computational modeling. In the natural world, some complex systems are discrete combinatorial systems—they use a finite number of discrete elements to create larger structures. Genetic codes, language, and perceptual phenomena are examples of systems in which discrete elements and a set of rules can generate a large number of meaningful entities that are quite distinct from those of their elements. A question of considerable importance is whether this fundamental characteristic of language and genetics is also a feature of the vertebrate motor system.

In the last few years, Bizzi and his colleagues have addressed the issue of whether simple units (motor primitives) exist that can be flexibly combined to accomplish a variety of motor tasks. The Bizzi lab has addressed this fundamental and long-standing question in experiments using spinalized frogs, rats, and monkeys. Recently, the group tested the hypothesis that linear combinations of muscle synergies represent a general mechanism for the construction of motor behavior. To this end, they have examined

several motor behaviors in intact, freely moving frogs. They recorded simultaneously from a large number of hind-limb muscles during locomotion, swimming, jumping, and defense reflexes and found that muscle activity patterns in each behavior could be reconstructed as linear combinations of a small number of muscle synergies. Moreover, some of the synergies were similar across different behaviors. Currently, they are investigating the way in which the CNS controls the hand movements of monkeys. The large number of muscles involved in the control of hand and finger movements and the variety of complex motor behaviors make the hand an ideal model for testing the validity of the modularity hypothesis. In the past year, the Bizzi laboratory published papers in a variety of academic journals describing how the modularity of the human motor system is affected by multiple sclerosis, novel techniques important to spinal cord function, and the modular organization of the spinal cord.

Emery Brown

Recent technological and experimental advances in the capability 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, Brown and his lab focus on developing statistical methods and signal-processing algorithms for neuroscience data analysis. Additionally, they are using a systems neuroscience approach to study how the state of general anesthesia is induced and maintained. To do so, they employ functional magnetic resonance imaging (fMRI), electroencephalography, neurophysiological recordings, microdialysis methods, and mathematical modeling in interdisciplinary collaborations with other BCS investigators as well as colleagues at the Harvard-MIT Division of Health Sciences and Technology, Massachusetts General Hospital (MGH), and Boston University. The long-term goals of this research are to establish a neurophysiological definition of anesthesia; create safer, site-specific anesthetic drugs; and develop better neurophysiologically based methods for monitoring the anesthetic state in real time.

In 2016, Brown and his lab published three research papers outlining key findings. The first, published in the *Proceedings of the National Academy of Sciences* (*PNAS*), outlines optogenetic methods to selectively activate dopamine neurons in the ventral tegmental area (VTA) to awaken rats from general anesthesia. These results provide strong confirmation for their previous work using intravenous Ritalin and electrical stimulation of the VTA to induce emergence from general anesthesia. This work reinforces the dopaminergic mechanism and provides strong basic science support for the Phase II clinical trial they are currently conducting in which they administer Ritalin at the end of surgery to awaken patients from general anesthesia. The second paper, also published in *PNAS,* explains how the Brown lab combined a state-space and multitaper paradigm to construct new algorithms for time-frequency analyses of non-stationary time series. The algorithm is highly computationally efficient and solves for the first time the inference problem in relation to non-stationary time series. The group characterized the properties of the algorithm in analyses of simulated data and actual experimental electroencephalogram data recorded in patients receiving general anesthesia. The algorithm can be applied broadly to any problem requiring time-frequency analysis of non-stationary data. The third paper, published in *Nature*, demonstrates in a rodent model of Alzheimer's disease that induced 40 Hz oscillations through visual stimuli

can reduce amyloid levels and improve behavior. This work has received a great deal of attention in the popular press as it may be readily adapted to the design of a potentially inexpensive and broadly applicable therapy for Alzheimer's disease.

Gloria Choi

Features central to perception in vision, touch, and hearing are topographically ordered in the sense organ, and this order is maintained from the periphery to primary sensory cortices. This has led to the prevailing view that early sensory processing in these sensory modalities is mediated by developmentally programmed neural circuits. In contrast, olfactory features cannot be meaningfully represented along continuous dimensions, and odorant responses in piriform display no spatial order. These observations have suggested a model in which piriform cells receive convergent input from random collections of glomeruli. As a consequence, odor representations can be afforded behavioral significance only after experience. The Choi lab's research addresses the mechanisms by which the brain learns to recognize olfactory stimuli and associate them with appropriate behavioral responses. Choi and her group will dissect the brain circuits underlying this learned behavior in an effort to understand how representations in piriform cortex can drive downstream targets to generate behavioral responses as a function of learning. They also plan to extend their approach to study social behavior, which in rodents is strongly affected by olfactory cues. One important modulator of social behavior is the hormone oxytocin, and the group plans to study how oxytocin may control the mechanisms by which animals learn to attribute social significance to olfactory stimuli.

Martha Constantine-Paton

The Constantine-Paton laboratory investigates the mechanisms involved in the development of synaptic plasticity, a phase of synaptogenesis during the development of the vertebrate brain in which the activity patterns of young neurons mediate a competition that allows only highly effective synapses to survive. These activity-dependent developmental events are responsible for many of the adaptive changes in brain wiring as children mature, and it is likely that they are also responsible for some of the devastating and permanent behavioral effects of genetically or environmentally caused disruptions in normal early brain activity. The lab's approach is to work both in vivo and in vitro, allowing normal developmental changes in brain structure or function to identify key molecular players that can subsequently be systematically studied in brain slices, dissociated primary neuron cultures, and intact animals. Recently, Constantine-Paton and her group have been focusing on processes that rapidly follow an important event in visual pathway development: eye opening. They have shown that the ability to produce long-duration increases in synaptic strength develops rapidly in the visual regions of the superior collciulus. Moreover, in layer IV of the visual cortex, these neurons that receive visual axons from the thalamus behave as if their synapses suddenly become fully potentiated: their post-synaptic evoked currents are generally larger than before eye opening and, in response to low-frequency long trains of stimulation, the cells show high levels of synaptic depression. Along with these functional changes, the group has found that the cortical projection to the superior colliculus refines within two days of eye opening and the onset of pattern vision. A continued activity-dependent structural (and also functional) plasticity is maintained for at least a week after eye opening, and the group is in the process of dissecting the mechanisms underlying this plasticity.

Additionally, the Constantine-Paton lab employs a multidisciplinary approach involving biochemistry and immunoprecipitation, immunocytochemistry, and vital imaging in tissue culture to identify and study the signaling molecules associated with the glutamate receptors in the "eye-opening interval." In 2016, Constantine-Paton began to collaborate with the Broad Institute proteomics units headed by Dr. Steven Carr. She and her group are conducting an ongoing study in which microRNAs that change in the eye-opening interval are compared with transcripts that change in the same interval to determine whether any of the synaptic plasticity events are under the control of microRNAs. The group is also currently involved in two collaborative projects in which they are applying their knowledge of developmental synaptic plasticity. One study involves electrophysiological and molecular experiments designed to identify the cellular basis of motoneuron death in a mouse model of amyotrophic lateral sclerosis (ALS). This study is being undertaken in collaboration with Dr. Robert Brown Jr. (MGH and Harvard Medical School), a leading ALS investigator. The other project involves genes known to be linked to schizophrenia and to NMDA (N-methyl-D-aspartate) receptor signaling. This investigation, undertaken in collaboration with Dr. Edward Skolnick's Psychiatric Disease Research Group based in the Broad Institute, uses small molecules known to inhibit neuregulin signaling to understand subsequent effects on NMDA receptor activity-dependent regulation.

James DiCarlo

The goal of DiCarlo's research group is a computational and mechanistic understanding of the brain mechanisms that underlie visual object and face recognition. They are focused on understanding how neuronal population transformations carried out in a series of brain processing stages—called the primate ventral visual stream—are effortlessly able to take incoming visual images and untangle object and face identity from confounding variables such as object position, scale, and pose. To build that understanding, the group collects data using large-scale neurophysiology, brain imaging, neural perturbation methods (e.g., optogenetics), and behavioral testing in human and non-human subjects and constructs and compares computational models that aim to emulate and predict those key empirical data. They have shown that the ventral stream conveys, at its top level, explicit neural population representations of other object latent variables such as position, size, and pose, and they have built a computational model that can quantitatively explain how those neural population patterns underlie behavioral reports of object identity, category, and other object variables. Over the past few years, the group has been the world's leading lab in showing how deep convolutional neural networks ("deep learning") inspired by ventral stream neuroanatomy can be used to explain many of these key empirical neural and behavioral phenomena. This approach is transforming visual systems neuroscience. Looking ahead, the group has recently shown that specific perturbations in the activity of small groups of high-level neurons lead to specific perturbations in perceptual reports. The DiCarlo lab ultimately aims to use this understanding to develop new computer vision systems, provide a basis for new neural prosthetics (brain-machine interfaces) to restore or augment lost senses, and discover how high-level visual representation is altered in human conditions such as agnosia, dyslexia, and autism.

Guoping Feng

Synapses are fundamental units of neuronal connectivity in the brain. It is at these specialized cell junctions that neurons communicate with one another. Many neuroscientists now look to the synapse for principles of learning and memory, for processes underlying behavior, and for pathological mechanisms of various neurological and psychiatric disorders. The long-term goals of the Feng laboratory are to understand the mechanisms regulating the development and function of synapses and to probe the roles of synaptic and circuitry dysfunction in certain abnormal behaviors and their relevance to psychiatric disorders. There are currently three major aspects of research in the lab. First, the group is interested in the molecular mechanisms regulating the assembly and function of the postsynaptic complex. Although hundreds of proteins have been identified at the postsynaptic complex, little is known about their in vivo functions at synapses. Using genetic approaches in mice, Feng and his group are dissecting the roles of key synaptic proteins in the assembly, maintenance, and plasticity of the postsynaptic complex. The second aspect of their research is focused on using genetic approaches in mice to dissect the molecular and cellular basis of behaviors. They are particularly interested in how changes in synaptic and circuitry function may lead to abnormal behaviors related to obsessive-compulsive disorder, autism, and schizophrenia/bipolar disorder. They apply a variety of mouse molecular genetic methods, such as regional and cell type–specific knock-out and knock-in approaches, to elucidate the molecules, neurons, and circuits involved in generating specific abnormal behaviors. The third line of research in the lab focuses on developing cutting-edge genetic tools for probing synaptic and circuitry function and dysfunction (e.g., transgenic mice expressing optogenetics for cell type–specific manipulation of neural activity and circuit function in living mice and transgenic mice expressing genetically encoded activity sensors for monitoring neuronal activity in vivo).

Recently, the Feng lab has been applying cutting-edge genome-editing technologies such as the CRISPR/Cas9 system to generate gene knock out and knock in in marmosets as a means of generating cell type–specific genetic tools and modeling neurological and psychiatric disorders. In 2016, using sophisticated genetic approaches in mice, the lab demonstrated for the first time that certain neurobiological defects and autistic-like behaviors in the Shank3 mouse model of autism are reversible in adult mice, exhibiting the plasticity of the adult brain and giving rise to hopes for developing effective treatments. Attention deficit and sensory dysfunction are common in many neurodevelopmental disorders. Feng and his group found that the thalamic reticular nucleus, which functions as an integrator, plays a key role in attention. They also discovered that modulation of thalamic reticular nucleus function is an effective treatment for attention deficit in the Ptchd1 mouse model of neurodevelopmental disorder.

Steven Flavell

The goal of Flavell's laboratory is to understand how neural circuits generate sustained behavioral states and how physiological and environmental information is integrated into these circuits. The problem of studying the interactions among neuromodulators, neural circuits, and behavioral states can be simplified in the nematode *Caenorhabditis elegans*. In addition to classical neurotransmitters, the *C. elegans* nervous system utilizes neuropeptides as well as biogenic amines such as serotonin and dopamine. The nervous system of *C. elegans* is a simple, well-defined model system: it contains

exactly 302 neurons, every neuron can be reproducibly identified in every animal, and a complete connectome has defined all of the synaptic contacts between these neurons. Flavell and his group use a variety of precise genetic tools to manipulate each neuron in this nervous system. By combining quantitative behavioral analyses with genetics, in vivo calcium imaging, and optogenetics, they have mapped out neural circuits that generate behavioral states and characterized the activity of neurons within these circuits during different states. Their current research aims to expand the knowledge of how neuromodulators such as serotonin organize the circuit-wide patterns of neuronal activity that emerge from these circuits as animals switch between behavioral states. They are also investigating how these neuromodulatory circuits integrate environmental and physiological cues that influence behavioral state generation.

In the last year, Flavell has made great strides in establishing his laboratory at MIT by recruiting members and setting up projects to which they can contribute. Progress during this period includes (1) completed construction of a microscope suitable for whole-brain imaging of freely moving *C. elegans*, (2) successful construction of a moving worm tracker that can measure every behavior that a single animal generates (e.g., feeding, movement) over its entire life span (this will be used to develop models of how behaviors are coordinated over time), (3) successful characterization of a novel ion channel that allows a sensory neuron to detect incoming food as it is being consumed, and (4) characterization of widespread gene expression changes in the *C. elegans* olfactory system caused by starvation, which may underlie starvation-induced behavioral changes.

John Gabrieli

The goal of the Gabrieli laboratory is to understand principles of brain organization that are consistent across individuals and those that vary across people due to age, personality, and other dimensions of individuality. Therefore, Gabrieli and his group examine brain-behavior relations across the life span. Their primary methods are brain imaging (functional and structural) and experimental behavioral studies of patients with brain injuries. The majority of their studies involve fMRI, but they also employ other brain measures as needed (e.g., electroencephalography) to address scientific questions. Much of their research occurs at MIBR's Martinos Imaging Center.

Edward Gibson

Research in the Gibson lab is aimed at investigating the characteristics of human languages; the relationship between culture and cognition, including language; and, most generally, how people learn, represent, and process language. The group uses a variety of methods, including behavioral experiments (e.g., reading and listening studies, dual-task experiments), statistical modeling, and corpus analyses. In collaboration with other labs, they also use fMRI, event-related potentials, and eye tracking. The major lines of research pursued in the lab include information processing and cross-linguistic universals. Accomplishments this year include a study demonstrating an advantage of being a second-language speaker: native speakers gave foreign-accented speakers the benefit of the doubt when interpreting their utterances. This is a novel finding in the face of a wealth of literature showing that people doubt the intelligence and trustworthiness of second-language speakers. In another study, Gibson and his group presented findings from the first tests of color naming among

the Tsimane, a remote Bolivian tribe living in the Amazon rain forest. Their results suggest that even people in cultures with few consensus color terms have access to full representations of color. Using an innovative information-theoretic analysis as an objective way to test for universal color-naming patterns, they found that all languages, including that of the Tsimane, transmit more information about warm colors than cool colors. In their first analysis of colors of objects identified by human observers, they showed that objects are more likely to have a warm than a cool color, providing the first causal explanation for a universal color-category distinction: color systems are optimized to communicate about colors of likely behavioral relevance.

Ann Graybiel

The Graybiel lab's research focuses on the basal ganglia, forebrain structures that are profoundly important for normal brain function but are also implicated in Parkinson's disease, Huntington's disease, obsessive-compulsive disorder, and addiction. The group's work is uncovering neural deficits related to these disorders, as well as the role the basal ganglia play in guiding normal behavior. Over the past year, the lab has developed a nonlinear multidimensional hidden state approach to complex neural circuit analysis; demonstrated that CalDAG-GEFI is essential for specific forms of neuroplasticity in the striatum, including the development of drug-induced sensitization of stereotypic behavior and long-term potentiation; and demonstrated that CalDAG-GEFI constitutive and conditional deletions in mice promote behavioral repetitiveness and affect a muscarinic cholinergic receptor-driven signaling pathway in the striatum.

Mark Harnett

Harnett and his group study how the biophysical features of individual neurons, including ion channels, receptors, and membrane electrical properties, endow neural circuits with the ability to process information and perform the complex computations that underlie behavior. They focus on the role of dendrites, the elaborate tree-like structures through which neurons receive the vast majority of their synaptic inputs. The thousands of inputs a single cell receives can interact in complex ways that depend on their spatial arrangement and on the biophysical properties of their respective dendrites. For example, operations such as coincidence detection, pattern recognition, input comparison, and simple logical functions can be carried out locally within and across individual branches of a dendritic tree. Harnett and his group address the hypothesis that the brain's computational power arises from these fundamental integrative operations within dendrites. They focus in particular on sensory processing and spatial navigation, with the goal of understanding the mechanistic basis of these brain functions. If integrative operations within neurons represent the building blocks for computations, plasticity in the biophysical properties of individual neurons could provide a potent means for either reinforcing or changing neural processing algorithms. Most current models of how the brain learns are based on the concept of spike-timing-dependent plasticity, in which the relative timing of action potentials in presynaptic and postsynaptic neurons causes synapses to become either stronger or weaker. The complexity of dendritic processing, however, suggests many other possible mechanisms through which the function of neural circuits could be altered by experience. The Harnett lab plans to explore these possibilities using electrical and optical recording in rodents and in vitro preparations to understand how changes in cellular properties lead to altered computations and, thus, to modification of behavior through learning.

In addition, cognitive disorders such as autism and intellectual disability are often characterized by changes in the number, distribution, and shape of dendritic spines, the tiny bud-like protrusions where the majority of excitatory synapses are located. Harnett and his group plan to study this directly using mouse genetic models of human brain disorders. By investigating how anatomical abnormalities alter dendritic operations, they hope to generate biophysical targets for experimental manipulation. The eventual goal is to causally link structural and functional changes at the cellular level with the aberrant computations that lead to pathological behaviors. This year they established two-photon in vivo imaging during awake virtual navigation in rodents and collected their first set of preliminary data; they are now collecting primary data. In addition, they have built the rest of the anatomical and physiological pipeline for this project and have constructed a new free behavior set-up with motion tracking as well as a first-generation prototype for head-fixed, mouse-actuated rotation. This prototype will be used with two-photon microscopy and in vivo patch clamp electrophysiology to maintain vestibular input, which will enable the group to answer critical questions in terms of neural integration and spatial navigation. The group has also built another two-photon in vitro electrophysiology rig to run parallel to their first one.

Myriam Heiman

The mammalian brain is composed of myriad cell types integrated into complex circuits. Complexity at the cellular level has historically hampered molecular studies of the mammalian nervous system. To help overcome this complexity and study the molecular profiles of distinct CNS cell types in situ, the Heiman lab makes use of the translating ribosome affinity purification (TRAP) methodology. TRAP combines cell type–specific expressions of transgenic proteins in genetically defined cell types with biochemical purification of translating ribosomes and their associated mRNAs. Heiman and her group use TRAP and other molecular biological methods to study the molecular mechanisms underlying various CNS degenerative diseases. One of the diseases they study is Huntington's disease (HD), a monogenic neurodegenerative condition caused by mutations in the huntingtin gene. In HD, medium-sized spiny neurons (MSNs) of the striatum are earliest and most dramatically affected, while many other cell types are much less affected. Through TRAP and genetic screening studies, the group recently identified genes that either enhance or suppress mutant huntingtin toxicity in MSNs, and they hope to use this knowledge to identify new therapeutic targets for HD. This year, Heiman and her colleagues finished their first round of genome-wide genetic screening for modifiers of mutant huntingtin toxicity in the mouse CNS.

In more hypothesis-driven research, Heiman and her group have found that Foxp2, a cortex and striatal-enriched transcription factor, modulates the toxicity of mutant huntingtin and that overexpression of Foxp2 can reverse many phenotypes seen in mouse models of HD. Also, they have developed a new molecular profiling methodology based on herpes virus retrograde labeling and RNA purification, and they have used this methodology to reveal that mutant huntingtin protein causes defects in transcription at the level of the mediator complex in vulnerable cell types in the cortex.

Neville Hogan

A central research question in the Hogan lab's research addresses the paradox of human performance: how are humans so much more dexterous and agile than robots despite vastly slower actuators, communication, and information processing? The approach of Hogan and his group emphasizes forceful interaction between the motor control systems of humans and machines. Their translational work pioneered therapeutic neurobotics to promote recovery after brain injury, and their research indicates that neural plasticity may be harnessed even long after injury—provided that the stimulation is appropriate. In addition, they have shown that human locomotion is remarkably sensitive to context. For example, while walking over ground as opposed to a treadmill, humans reduce their margin of stability, enabling greater efficiency. The Hogan group's research demonstrates that even in simple reaching tasks, humans find it very difficult to move slowly, which supports their theory that the superiority of human control is based on primitive dynamic actions.

Mehrdad Jazayeri

When we think of behavior, we think of neural code, and when we think of neurons and neuronal networks, we think of neural dynamics. The link between brain and behavior thus resides at the intersection between the neural code and neural dynamics. The long-term objective of research in the Jazayeri lab is to understand (1) how neurons and neural circuits generate and control dynamic patterns of activity and (2) how those patterns encode behaviorally relevant information. Jazayeri and his group tackle these question by performing experiments on animals trained to perform a wide array of cognitive tasks that require anticipation, integration, coordination, and timing—functions that depend on the brain's internally generated dynamics. They combine psychophysics, electrophysiology, optogenetics, machine learning, and computational modeling to uncover the mechanisms that shape neural dynamics and the principles that put those dynamics to use in the control of behavior. This year the Jazayeri lab found a compelling answer to a long-standing question in neuroscience, that of how the brain tracks time. Previous work in this domain has emphasized clocks, oscillators, and chaotic neural activity patterns. The work of the Jazayeri lab rules out these models and points to an elegant and unsuspected alternative. Specifically, the lab found that the brain produces different time intervals by adjusting the speed with which neural responses unfold over time.

Nancy Kanwisher

The Kanwisher laboratory investigates the functional organization of the brain as a window into the architecture of the human mind. In the past, the lab has discovered a number of cortical regions specialized for specific cognitive tasks such as perception of faces, places, bodies, and words. Current work is attempting to better characterize the function of each of these regions, to test long-standing but unresolved claims of other cortical specializations (e.g., for language), and to search for new unpredicted specializations using novel clustering methods (in collaboration with Polina Golland). More generally, Kanwisher and her group want to know which mental functions get their own specialized piece of cortical territory and why we have cortical regions specialized for some mental functions but apparently not others. A major goal of their current

research is to understand how functionally specific cortical regions arise in development, as well as whether and how they change in adulthood. They have demonstrated important roles for experience by showing (1) changes in the cortical representation of objects after training, (2) the existence of a cortical region whose specialization (for visual word perception) must be based on experience, and (3) changes in the retinotopic cortex response among people with loss of foveal vision due to macular degeneration.

In a new line of work funded by the Ellison Medical Foundation, Kanwisher and her group (in collaboration with Professor Gabrieli, Professor Rebecca Saxe, and other colleagues) are beginning longitudinal studies of brain and behavior in typical children and children with autism. A central puzzle in this work is why the cortex continues to change into the teenage years even when the relevant underlying cognitive functions appear to be in place by age four. Other lines of work in the lab explore the nature of the representations that enable us to recognize faces, objects, words, and scenes; the neural representation of visual arrays of multiple objects; the perceptual/cognitive functions that persist during diminished states of consciousness; and the role of retinotopic cortex feedback in visual information processing.

Roger Levy

The Levy lab's research focuses on theoretical and applied questions in the processing and acquisition of natural language. This year, the lab completed a project on automated discovery of non-arbitrary form-meaning correspondences in human language. Traditionally, language scientists have considered form meaning arbitrary: the word "dog," for example, sounds nothing like its counterparts in Spanish (perro) or Japanese (inu). But exceptions have long been known anecdotally; in English, for example, words starting with "gl" often relate to light (glimmer, glow, glisten, glean). Levy and his group developed a method that automatically discovers these systematicities from a corpus. In addition, they ran a series of psycholinguistics studies using the 2016 presidential campaign as a natural experiment manipulating Americans' expectations regarding the gender of the then-hypothetical next president. Before the election, increasing beliefs in a female future president manifested as changes in language comprehension and production behavior. However, Levy and his group also found residual gender bias: although for much of this period participants believed that the next president was more likely to be female than male, references to the future president with the female pronoun "she" led to measurable processing difficulty relative to "he" references. This type of time-series study is highly novel in psycholinguistics; the success of the Levy lab's investigation opens the door to a range of future possible studies.

Yingxi Lin

The Lin laboratory studies the development of inhibitory circuits in the brain. As in a conventional electrical circuit, the brain uses both positive and negative components to amplify desirable signals while maintaining the overall stability of the system. An outstanding question in neurobiology is how the balance between excitation and inhibition is established and maintained. The underlying molecular mechanisms are not well understood, but inhibitory neurons and their connections, which are readily modified by activity, are likely to play a critical role. Impaired inhibition has been implicated in many brain disorders, including epilepsy, anxiety disorders,

schizophrenia, and autism. A key ingredient of the answer to this question is the regulation of gene expression in response to neural activity. The work of Lin and her group in this space revealed a novel transcriptional pathway involved in activity-regulated GABAergic synapse development, offering a unique opportunity to unravel the mechanism by which neural activity regulates inhibitory synapses and the balance between excitation and inhibition. They are building on this work and focusing on understanding how neuronal activity regulates the development and function of both inhibitory synapses and inhibitory neurons. They use forward genetics to identify transcription programs that are important for the development of inhibitory circuits, followed by a combination of molecular, biochemical, electrophysiological, and mouse genetic approaches to extend gene discovery to an in-depth understanding of the molecular mechanisms underlying inhibitory circuit development and function. Their research will also address fundamental questions in neuroscience and identify potential therapies for neurological disorders.

The main interest of Lin's lab is exploring the cellular and molecular mechanisms by which neuronal activity is coupled to modifications of neural circuits that lead to long-term behavioral changes. In the past few years, they have been developing a versatile neuronal activity mapping system to map the neuronal ensembles involved in encoding experiences. Building on the mapping system, they are now investigating distinct neuronal ensembles defined by different molecular and cellular events. The existence of distinct active neuronal ensembles has never been identified at the molecular level. In addition, they wrapped up an exciting study in which they found the molecular mechanism critical for the sparse connectivity between the dentate gyrus and CA3, predicted to be critical for encoding contextual memory in computational modeling but never shown experimentally. Finally, they are in the process of building a neuronal activity atlas of the developing mouse brain.

J. Troy Littleton

The computational power of the brain depends on synaptic connections that link together billions of neurons. The Littleton laboratory focuses on understanding the mechanisms by which neurons form synaptic connections, how synapses transmit information, and how synapses change during learning and memory. To complement this basic research in neuroscience, they also study how alterations in neuronal signaling underlie several neurological diseases, including epilepsy, autism, and Huntington's disease. They combine molecular biology, protein biochemistry, electrophysiology, and imaging approaches with *Drosophila* genetics to address these questions. A major goal for the next decade of neuroscience research is moving beyond genomic data to determine how proteins specify the distinctive signaling properties of neurons and enable them to interconnect in computational circuits that dictate behavior. Despite the dramatic differences in complexity between *Drosophila* and humans, genomic analyses have confirmed that key neuronal proteins and the functional mechanisms they govern are remarkably similar. As such, Littleton and his group are attempting to elucidate the mechanisms underlying synapse formation, function, and plasticity using *Drosophila* as a model system. By characterizing how neurons integrate synaptic signals and modulate synaptic growth and strength, they hope to bridge the gap between molecular components of the synapse and the physiological responses they mediate.

In a *Journal of Neuroscience* article published in 2016, Littleton and lead author Kathryn Harris (a BCS postdoctoral associate) described their new findings showing that mutations in the *Drosophila* Shank homolog disrupt synaptic wingless/Wnt signaling by altering postsynaptic receptor internalization. Given that mutations in the Shank homolog are a major cause of autism in humans, their findings in the *Drosophila* model suggest that Shank proteins play critical roles in mediating protein trafficking from the postsynaptic compartment. Additionally, Littleton and former BCS graduate student Megan Krench generated a new *Drosophila* model of the neurodegenerative disorder Huntington's disease-like 2 (HDL2) (the details were published in *Human Molecular Genetics* in 2016). They found that unlike what occurs in the similar polyglutamine expansion disorder Huntington's disease, where mutant proteins aggregate in the cytoplasm and disrupt axonal transport and normal synaptic growth, protein aggregates in HDL2 form in the nucleus. They went on to demonstrate that lethality associated with this disease requires nuclear accumulation of the protein and that redirecting the polyglutamine expanded HDL2 protein to the cytoplasm prevents lethality and disease progression.

Josh McDermott

The McDermott laboratory studies how people hear. Sound is produced by events in the world, travels through the air as pressure waves, and is measured by two sensors (the ears). The brain uses the signals from these sensors to infer a vast number of important things: what someone said, their emotional state when they said it, and the whereabouts and nature of events we cannot see, to name but a few. Humans make such auditory judgments hundreds of times a day, but their basis in our acoustic sensory input is often not obvious and reflects many stages of sophisticated processing that remain poorly characterized. McDermott and his group seek to understand the computational basis of these impressive yet routine perceptual inferences. They hope to use their research to improve devices for assisting those whose hearing is impaired and to design more effective machine systems for recognizing and interpreting sound, given that such systems at present perform dramatically worse in real-world conditions than do normal human listeners. Their work combines behavioral experiments with computational modeling and tools for analyzing, manipulating, and synthesizing sounds. They draw particular inspiration from machine hearing research: they aim to conduct experiments that reveal how humans succeed where machine algorithms fail and to use approaches in machine hearing to motivate new experimental work.

The research conducted by McDermott and his group also has strong ties to auditory neuroscience. Models of the auditory system provide the backbone of their perceptual theories, and they collaborate actively with neurophysiologists and cognitive neuroscientists. The lab thus functions at the intersection of psychology, neuroscience, and engineering. In current research, the lab is exploring how humans recognize real-world sound sources, segregate particular sounds from the mixture that enters the ear (the cocktail party problem), separate the acoustic contribution of the environment (e.g., room reverberation) from that of the sound source, and remember and/or attend to particular sounds of interest. They also study music perception and cognition, both for their intrinsic interest and because music often provides revealing examples of basic hearing mechanisms at work.

Earl Miller

Miller and his group use experimental and theoretical approaches to study the neural basis of the high-level cognitive functions that underlie complex goal-directed behavior. Their focus is on the frontal lobe, the region of the brain most elaborated in humans and linked to neuropsychiatric disorders. They have provided insights into how categories, concepts, and rules are learned; how attention is focused; and how the brain coordinates thought and action. In addition, they have innovated techniques for studying the activity of many neurons in multiple brain areas simultaneously, which has offered insight into how different brain structures interact and collaborate. This work has established a foundation upon which to construct more detailed, mechanistic accounts of how executive control is implemented in the brain and its dysfunction in diseases such as autism, schizophrenia, and attention deficit disorder. The Miller lab made a discovery last year that has the potential to overturn 50 years of scientific dogma. Working memory is probably the most studied cognitive function. For the past several decades, neuroscientists have believed that as information is held in working memory, brain cells associated with that information fire continuously. However, a new study by the Miller lab has upended that theory, instead showing that as information is held in working memory, neurons fire in sporadic, coordinated bursts. The results of this investigation support a model in which working memories are held in temporary changes in synaptic weights, induced by spiking.

Elly Nedivi

The capacity of the brain to modify connections in response to the environment is termed plasticity. Plasticity is a prominent feature of brain development, and it underlies adult learning and memory and adaptive reorganization of sensory maps. To understand the cellular mechanisms that underlie brain plasticity, Nedivi's laboratory is identifying and characterizing the participating genes and the function of the proteins they encode. This work began with the cloning of a large number of activity-regulated genes they termed candidate plasticity genes (CPGs). Although only a small subset of these genes have been pursued to date, it is clear that the pool is highly enriched for genes that are relevant to neuronal and synaptic function. One CPG characterized in depth, CPG2, has emerged as a key component of a specialized postsynaptic endocytic mechanism devoted to internalization of synaptic proteins, including glutamate receptors. The gene encoding CPG2 was recently identified in a genome-wide association study screen as a risk gene for bipolar disorder. Another, CPG15, plays a dual role in the brain: as a survival factor that rescues cells from apoptosis and as a growth and differentiation factor that affects process outgrowth and synaptic maturation. Motivated by the large number of CPGs that affect neuronal structure, the group 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. Nedivi's lab was the first to show unambiguous evidence of dendritic growth and retraction and of branch tip additions in the adult brain. Their data singled out GABAergic interneurons as those capable of structural dynamics, suggesting that circuit rearrangement is restricted by cell type–specific rules. Recently, they have also developed methods for labeling and chronic monitoring of excitatory and inhibitory synapses across entire neuronal arbors in the mouse visual cortex in vivo.

A large part of the lab is now devoted to imaging-related projects, some associated with characterization of CPG function in vivo and others addressing more general questions related to structural plasticity of cortical circuitry, with a focus on inhibitory components. The Nedivi lab has recently observed a new reversible type of synapse dynamics unique to inhibitory synapses, which could provide flexible, input-specific gating of stable excitatory connections. Researchers in the lab have also identified a new component of the endocytic complex, EndoB2, that partners with CPG2 to facilitate internalization of glutamate receptors, a key mechanism for regulating synaptic strength. Finally, Nedivi lab scientists have characterized the region of the human SYNE1 gene homologous to rat CPG2, and their results show that it encodes a localized protein that is functionally interchangeable with rat CPG2. This suggests that human SYNE1, a risk gene for bipolar disorder, plays a role in regulating glutamatergic synaptic function.

Tomaso Poggio

The issue of intelligence is not only one of the great issues in science but probably the greatest of all. The scientific goal of Poggio and his group is to advance the science and engineering of intelligence. By integrating technological breakthroughs in neuroscience, continued rapid advances in computer power, and accumulated knowledge in machine learning and cognitive science, they hope to make a significant leap in scientific understanding of human intelligence and its neural basis that could also advance our ability to replicate intelligence in engineered systems. Poggio's aim as the director of the Center for Brains, Minds, and Machines is to create a new field by bringing together computer scientists, cognitive scientists, and neuroscientists to work in close collaboration. This new field—the science and engineering of intelligence—would be dedicated to developing a computational understanding of human intelligence and to establishing engineering practices based on that understanding.

In one of the highlights from the past year, the Poggio lab extended hierarchical models of the ventral stream to include the eccentricity dependence of resolution in the visual cortex. Additionally, the lab has obtained theoretical results on conditions under which deep networks can be exponentially better than shallow networks.

Rebecca Saxe

Externally observable components of human actions carry only a tiny fraction of the information that matters. Human observers are vastly more interested in perceiving or inferring the mental states—the beliefs, desires, and intentions—that lie behind the observable shell. If a person checks her watch, is she uncertain about the time, late for an appointment, or bored with the conversation she is engaged in? If a person shoots his friend on a hunting trip, did he intend revenge or just mistake his friend for a partridge? The mechanism people use to infer and reason about another person's states of mind is called a "theory of mind" (ToM). One of the most striking discoveries of recent human cognitive neuroscience—made in the Saxe lab and others—is that there is a group of brain regions in the human cortex that selectively and specifically underlie ToM. Excitingly, most questions about these brain regions remain open. The Saxe lab explores ToM as a case study involving a deeper and broader question: how does the brain, an electrical and biological machine, construct abstract thoughts? Saxe and her colleagues use functional neuroimaging, behavioral studies with children and adults, patient

studies, and transcranial magnetic stimulation to examine abstract representations in the human brain. In addition to ToM, their recent research has investigated brain development, moral reasoning, causal reasoning, and language.

Laura Schulz

The infrastructure of human cognition—our commonsense understanding of the physical and social world—is constructed during early childhood. The Schulz lab studies the representations and learning mechanisms that underlie this feat. Their research looks at (1) how children infer the concepts and causal relations that enable them to engage in accurate prediction, explanation, and intervention; (2) the factors that support curiosity and exploration, allowing children to engage in effective discovery; and (3) how social-communicative contexts (e.g., demonstrating evidence, explaining events, disagreeing about hypotheses) affect children's learning. Recent work in the lab has focused on the kinds of inferential processes that underlie early social cognition, including children's reasoning about their own and others' emotions, motivations, and competencies. Computational models of human cognition inform much of the research in the lab. Schulz and her group are especially interested in understanding trade-offs in the inferential process, such that the same inductive biases that constrain the hypothesis space and allow us to draw rich inferences from sparse data can also make it difficult for us to revise our beliefs. This paradox poses a challenge for educators but also provides insight into the factors that might promote effective learning and teaching.

Most of the research in the lab involves babies and children. Since babies and children have limited prior knowledge and no formal training, understanding how children reason about the world can give us insight into the origins of knowledge and fundamental principles of learning. Understanding learning in early childhood also has the potential to support innovations in teaching and education. Schulz and her group have on-site laboratories at the Boston Children's Museum and have recently launched a new online developmental lab (Lookit!) that enables families to participate in self-directed research from their homes. They use a variety of approaches in their studies, ranging from infant looking time methods to free-play paradigms. A number of studies, including many from their own lab, have suggested that children selectively engage in search, question asking, and exploratory play when the probability of information gain is higher. In a recent investigation, they showed that there is a fine-grained, quantitative mapping between the extent of children's exploratory play and the difficulty of the discriminations they are trying to make. Because children heard only a single sound at a time, their estimate of the difficulty of the discrimination problem had to come from an internal computation of the uncertainty about the perceptual data relative to the alternative hypotheses. This suggests that children's exploratory play quantitatively tracks the discriminability of alternative hypotheses.

Pawan Sinha

Research in the Sinha laboratory focuses on understanding how the brain recognizes objects in the visual world using a combination of experimental and computational modeling techniques. Sinha and his group address the nature of the object representations in the brain and how these representations can be learned from visual experience. They investigate the first component by examining the nature of

information that the brain uses for recognizing important classes of objects such as faces and, particularly, impoverished images such as highly blurred photographs and minimalistic caricatures. Analyzing such stimuli promises to provide insights about the aspects of image information that may be critical and/or sufficient for recognition. The lab's research on object learning involves work with a unique population of children in India who have gained sight after several years of congenital blindness. Studies of the time course of visual skill development in these children provide valuable clues for the lab's ongoing efforts to computationally model acquisition of object concepts by the human brain. This work has also had an unexpected bearing on understanding the causal underpinnings of autism. The lab has developed a theoretical model of a core impairment that can help explain multiple aspects of autism. Empirical testing of the theory's predictions is currently under way.

The past year has yielded a number of accomplishments for the Sinha lab. Data from a multi-year study have allowed the lab to compellingly argue against a putative critical period for acquiring the face/non-face visual distinction. Neuroimaging studies that have proceeded concurrently with behavioral assessments of face learning have allowed the group to make long-sought-after structure-function correlations between cortical activations and face categorization skills. Additionally, the Sinha lab developed a theoretical explanation for the puzzling observation that even a few months of visual deprivation lead to compromised face identification skills. Their explanation has greater parsimony than past accounts assuming a critical period for face processing because it is based exclusively on the nature of the experienced visual input. It has implications for understanding features of normal visual development as well as potential interventions for disorders such as prosopagnosia. To better understand the neural dynamics of face recognition, Sinha and his collaborators collected magnetoencephalography data from several individuals while they viewed familiar or unfamiliar faces. Sophisticated pattern classification analyses yielded a remarkable result: the familiar/unfamiliar face distinction emerges within the cortex as early as 100 milliseconds after stimulus onset. This is far less than the 250-millisecond period that had been assumed thus far and raises important questions regarding the computations underlying face individuation in the normal brain. Finally, the lab's theory of a core deficit in autism continues to be influential, spurring studies in domains ranging from molecular biology to cognitive science. It has also allowed the group to forge exciting collaborations within MIT and across multiple institutions (including Yale and Northeastern) to test the theory's predictions.

Mriganka Sur

Sur's laboratory studies the plasticity, development, and dynamics of the cerebral cortex using a rich combination of systems and approaches. The developing brain wires itself through a genetic blueprint that is also acutely sensitive to the environment. The adult brain utilizes these circuits to generate internal models that are crucial for transforming sensory input into action. The primary goal of the laboratory is to understand long-term plasticity and short-term dynamics in networks of the developing and adult cortex. A related goal is to use these insights to discover mechanisms underlying disorders of brain development. The Sur lab uses microarrays and proteomics analyses to discover molecules that underlie cortical patterning and plasticity, along with molecular and physiological tools to examine the function of these genes and their

interactions with the environment. Additionally, Sur and his group use several model systems for studying developmental plasticity and its mechanisms. One, which they pioneered, involves rewiring the brain: they induce projections from the eye to innervate nonvisual centers, such as the auditory thalamus, early in life. Visual inputs cause the auditory pathway to develop with a very different pattern of activity than normal. This profoundly alters neuronal circuits and connectivity in the rewired auditory cortex. A second model system involves the formation and maintenance of ocular dominance columns in the visual cortex. Here the lab defines rules of plasticity by examining molecular mechanisms and dynamics of rapid structural and functional changes in synapses. Specific molecules such as Arc, CaMKII, and actin are key players that link feed-forward and feedback changes in neuronal connectivity due to changes in electrical activity. The lab uses cell-specific markers combined with detailed two-photon measurements of single-cell responses to analyze the roles of inhibitory and excitatory neuron subtypes, along with astrocytes, in visual cortex circuits. Using mice performing specific behavioral tasks, the lab employs advanced recording methods, computational analyses, and optogenetic manipulations to define information flow and sensory-motor transformation in the visual, parietal, and frontal cortex.

Additionally, the Sur laboratory uses animal models of subsets of autism, such as Rett syndrome, to discover mechanisms by which the underlying genes influence synaptic plasticity and neuronal dynamics. Novel therapeutics arising from these approaches have entered clinical trials. This year, the lab investigated the role of visual (V1), posterior parietal (PPC), and frontal motor (fMC) cortices in sensorimotor mapping in mice during performance of a memory-guided visual discrimination task. Large-scale calcium imaging revealed that V1, PPC, and fMC neurons exhibited heterogeneous responses spanning all task epochs (stimulus, delay, response). Population analyses demonstrated unique encoding of stimulus identity and behavioral choice information across regions, with V1 encoding the stimulus, fMC encoding choice even early in the trial, and PPC multiplexing the two variables. Optogenetic inhibition during behaviors revealed that all regions were necessary during the stimulus epoch, but only fMC was required during the delay and response epochs. Stimulus identity can thus be rapidly transformed into behavioral choice, requiring V1, PPC, and fMC during the transformation period but only fMC for maintaining the choice in memory prior to execution.

Josh Tenenbaum

Tenenbaum and his group study the computational basis of human learning and inference. Through a combination of mathematical modeling, computer simulation, and behavioral experiments, their goal is to uncover the logic behind our everyday inductive leaps: constructing perceptual representations, separating “style” and “content” in perception, learning concepts and words, judging similarity or representativeness, inferring causal connections, noticing coincidences, and predicting the future. They approach these topics with a range of empirical methods—primarily behavioral testing of adults, children, and machines—and formal tools drawn chiefly from Bayesian statistics and probability theory but also from geometry, graph theory, and linear algebra. Their work is driven by the complementary goals of trying to achieve a better understanding of human learning in computational terms and trying to build computational systems that come closer to the capacities of human learners. This year,

they have continued to develop their work on reverse engineering human perception, cognition, and learning using probabilistic programs and program induction. They have built new state-of-the-art models of how people perceive the three-dimensional structure of objects and their physical properties using a combination of deep neural networks for recognition and probabilistic generative models based on video game engines for efficient, approximate graphics and physical simulation. They have also built models of how people infer the beliefs, desires, percepts, plans, and intelligence of other agents based on probabilistic inversion of planning engines. Finally, they have constructed models of how people learn new concepts, theories, and word meanings using techniques of program induction and program synthesis.

Susumu Tonegawa

The main research interest in Tonegawa's laboratory is deciphering brain mechanisms subserving learning and memory. They seek to understand what happens in the brain when a memory is formed, when a fragile short-term memory is consolidated into a solid long-term memory, and when a memory formed previously is recalled on subsequent occasions. They also seek to understand the role of memory in decision making and how various external or internal factors (e.g., reward, punishment, attention) affect learning and memory. In summary, they study how the central nervous system in the brain enables our mind, with a focus on learning and memory.

Because many of the fundamental processes of and neuronal mechanisms for memory are expected to be shared among mammals, and a vastly greater variety of experimental procedures are available for rodents than humans, they use laboratory mice as the primary model for memory research. With mice or other animals, memory can be monitored only through behaviors. At the same time, researchers must identify the crucial events and processes that are ongoing inside the brain, permitting the specific and diverse aspects of learning and memory. This latter task is the challenge for memory researchers and neuroscientists in general because the brains of higher organisms are incredibly complex. In order to meet this challenge, Tonegawa and his group employ highly specific genetic manipulation techniques, creating mutant mouse strains in which a specific gene—and hence its gene products, such as neurotransmitter receptors and enzymes—is deleted or inactivated only in a specific type of cell (spatial restriction) and/or a specific period of a behaviorally defined learning or memory process (temporal restriction). This year, Tonegawa's lab conducted a study showing that memories assumed to be lost in the early stages of Alzheimer's disease in fact remain and can even be elicited via optogenetic stimulation. The revelation that memories previously thought lost are in fact still harbored in the brain offers hope in itself, but the ability to elicit these memories using optogenetic stimulation offers hope for potential future treatments of this disease in humans. The group also conducted the first study pinpointing the storage location of social memory in the hippocampus; although the hippocampus had previously been assumed to be a storage location, they showed that social memories are stored in the vCA1 brain area and accessed through a neural circuit connecting the vCA1 area with the nucleus accumbens.

Kay Tye

The Tye lab employs a multidisciplinary approach including optogenetic, in vivo, and ex vivo electrophysiological, pharmacological, and imaging techniques to find mechanistic explanations for how emotional and motivational states influence behavior. This year, Tye and her group lab identified a neural substrate related to the experience of social isolation, or a loneliness-like state. The strength of synapses onto dopamine neurons in the DRN (dorsal raphe nucleus) was increased when they socially isolated mice for 24 hours. The activity of these neurons increases when an animal is exposed to a social agent after isolation but not when the animal is currently residing in a group, which they showed using a genetically encodable calcium indicator selectively expressed in DRN dopamine neurons. Activating these neurons increased social preference while producing a negative affective state, and inhibiting the neurons suppressed an isolation-induced rebound of social interaction. The group also sought to understand how structure is related to the positive and negative valence-encoding properties of amygdala neurons. They found that neurons sending information to different targets had distinct population characteristics but still exhibited response heterogeneity within each population. In addition, they elucidated a circuit mechanism by which the lateral hypothalamus disinhibits ventral tegmental area dopamine neurons to drive a variety of motivated behaviors.

Matthew Wilson

Wilson's laboratory studies the neural processes within the hippocampus and neocortex that enable memories to form and persist over long periods of time. They use a technique that allows them to simultaneously record the activity of hundreds of individual neurons across multiple brain regions in freely behaving animals. When combined with genetic, pharmacological, and behavioral manipulations, these recordings allow them to gain a mechanistic understanding of how animals learn and remember. Currently, an important focus of the laboratory is the reactivation of sequential activity in neural ensembles during waking and sleep. Because many cells in the hippocampus represent specific locations, the lab can use their firing patterns to reconstruct movement trajectories being "replayed" during periods of rest. The function of such replay is not well understood, but it may be involved in memory consolidation or even in action planning. Wilson and his group also study the interplay between the hippocampus and other brain regions, such as the prefrontal cortex, cingulate cortex, thalamus, and ventral tegmental area. Understanding how activity is coordinated between multiple areas is likely to be crucial for understanding how memories are stored and retrieved. Recent advancements include motorized microdrives for improving tetrode yield and stability, a system for real-time feedback during experiments, and new computational tools for analysis of neural activity. Taken together, these approaches contribute to the lab's overall research objective: to understand the link between neural ensemble representations and cognitive capabilities. This year, the lab developed novel tools that allow real-time decoding of neural activity patterns associated with memory reactivation during quiet wakefulness and sleep. This can be combined with closed-loop optogenetic control systems that allow real-time manipulation of brain activity associated with specific memory patterns in order to explore the detailed mechanisms of memory encoding, retrieval, and consolidation.

Weifeng Xu

The Xu laboratory is interested in how neurons respond to external stimuli and induce changes in their properties that eventually lead to encoding of the information in the neural circuit. The focus of the lab is on the glutamatergic synaptic transmission, which underlies feed-forward excitatory information processing. So-called synaptic plasticity (long-lasting changes in excitatory synaptic strength) is thought to be the cellular substrate for learning and memory. Membrane excitability and intracellular environment respond to incoming neural activity and fluctuate at different temporal domains with potentially different spatial constraints. These fluctuations can influence the induction and expression of synaptic plasticity. Xu and her group are interested in how these changes are coordinated and modulated and eventually lead to circuit modification and successful coding of incoming information. To answer these questions, they use multi-level analyses combining molecular biology, biochemistry, electrophysiology, and behavioral approaches to investigate the functional roles of particular gene targets in regulating neural plasticity at the cellular level and learning and memory at the behavioral level. The NMDA receptor–dependent synaptic plasticity mechanism has been proposed as the cellular substrate for experience-dependent modification of the excitatory circuit in development and in learning and memory. Several outstanding and essential questions are as follows: (1) How is NMDA receptor–mediated Ca influx (and consequently Ca/CaM dynamics) regulated to control the directionality of synaptic plasticity? (2) What molecular substrates are critical for the control mechanism? and (3) How does the synaptic plasticity mechanism shape synaptic connectivity in development and in learning and memory? The lab's studies have revealed the pivotal role of neurogranin in controlling the synaptic plasticity threshold and the developmental plasticity of the cortical circuit.

Feng Zhang

The Zhang lab is designing new molecular tools for manipulating the living brain using optogenetics. Zhang is a leader in the development of the CRISPR-Cas9 system, a genome editing technology that allows scientists to make precise changes to a DNA sequence. This scientific advance is expected to transform many areas of biomedical research and may ultimately form the basis of new treatments for human genetic diseases. By applying these and other methods, Zhang and his group hope to generate new animal models of human diseases in order to study their underlying biological mechanisms. They are especially interested in complex disorders, such as psychiatric and neurological diseases, that are caused by multiple genetic and environmental risk factors and are difficult to model using conventional methods. Zhang's method may also lead to new ways to produce brain stem cells, which could be used as a platform for developing new drugs and as a source of material for transplantation in many human degenerative diseases. The heterogeneity of brain tissue necessitates new methods that allow researchers to measure the unique transcriptional states of individual neurons. Toward this end, the Zhang lab is developing novel single-neuron sequencing technologies that can be applied to neural tissues.

Efforts over the past year centered on advancing CRISPR technology and understanding. The lab discovered and characterized C2c2, the first single-component RNA-guided/ RNA-targeting CRISPR effector. This discovery establishes a new and long-sought-after

platform for the development of novel RNA-targeting molecular tools. Additionally, Zhang and his group reported the first crystal structure of CRISPR-Cpf1, which paves the way for the development of Cpf1-based genome editing technologies. They also developed an approach to use CRISPR-Cas9 in conducting high-throughput interrogations of the function of non-coding sequences in the genome with single-base resolution. This approach enables researchers to identify regulatory elements in the genome that play important roles in controlling gene expression. The majority of genome-wide variations that affect disease risk fall in non-coding regions, and this approach makes it possible to study the effects of those genetic variations. Finally, the lab developed a method to sequence the transcription of individual neurons and applied it to study the diversity of brain cell types as well as the transcriptional changes that underlie neuronal differentiation and maturation.

Selected Awards and Honors

- Associate Professor Edward Boyden was named a faculty scholar by the Howard Hughes Medical Institute, the Simons Foundation, and the Bill and Melinda Gates Foundation. In addition, Professor Boyden and Professors Earl Miller, Elly Nedivi, and Molly Potter were elected to the American Academy of Arts and Sciences.
- Assistant Professor Kwanghun Chung received the NIH New Innovator Award.
- Professor Michale Fee received the Fundamental Science Investigator Award and the School of Science Prize for Undergraduate Education.
- Professor Edward Gibson was presented the BCS Award for Excellence in Undergraduate Advising.
- Mark Harnett was named Frederick A. (1971) and Carole J. Middleton Career Development Assistant Professor of Neuroscience.
- Myriam Heiman was named Latham Family Career Development Assistant Professor. Also, Professor Heiman and Professors Earl Miller and Pawan Sinha each received a Paul and Lilah Newton Brain Science Award.
- Assistant Professor Mehrdad Jazayeri was the recipient of a 2017 McKnight Scholar Award.
- Troy Littleton received the Menicon Professor in Neuroscience chair. In addition, Professor Littleton received the BCS Award for Excellence in Postdoctoral Mentoring.
- Professor Earl Miller received the Goldman-Rakic Prize for Outstanding Achievement in Cognitive Neuroscience from the Brain and Behavior Research Foundation.
- Professor Molly Potter received the Norman Anderson Lifetime Achievement Award from the Society of Experimental Psychologists.
- Professor Rebecca Saxe received the BCS Award for Excellence in Undergraduate Teaching and the BCS Award for Excellence in Graduate Mentoring.

- Professor Li-Huei Tsai was presented the Society for Neuroscience Mika Salpeter Lifetime Achievement Award.
- Assistant Professor Kay Tye received the Society for Neuroscience's Young Investigator Award and the Brain and Behavior Research Foundation's Freedman Prize for Exceptional Basic Research.
- Feng Zhang was named James and Patricia Poitras Professor in Neuroscience; was a runner up for Time magazine's person of the year; was named a faculty scholar by the Howard Hughes Medical Institute, the Simons Foundation, and the Bill and Melinda Gates Foundation; and received tenure at MIT.

James J. DiCarlo
Department Head and Professor