Spring/Summer 2019

bcsnews

Demystifying Disorder

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brain+cognitive sciences

BCS Leadership

Michale Fee, PhD
Glen V. and Phyllis F. Dorflinger Professor of Neuroscience
Associate Department Head of Education, BCS

Rebecca Saxe, PhD
John W. Jarve (1978) Professor in Brain and Cognitive Sciences
Associate Department Head, BCS

On the Cover

Researchers in Guoping Feng's lab have stained neurons in the mouse brain to reveal a protein related to autism and other brain disorders. Image: Michael Wells and Guoping Feng. **View the full story on page 4.**

Dear Friends,

As a Department, basic science is our strength, as this is the key to advances across applications ranging from detection, prevention and treatment of disorders of the mind, to next-generation artificially intelligent systems, to improvements in how we educate our children. Our incredible community is making real progress on our overarching mission — "to reverse engineer the mechanisms of the mind."

For this special issue, we focus on an area of research with overwhelming societal impact: disorders of the mind. The BCS Complex (a.k.a. MIT Building 46) is currently the hub of several important collaborative activities in this space, including the Hock E. Tan and K. Lisa Yang Center for Autism Research, the Poitras Center for Psychiatric Disorders Research, the Simons Center for the Social Brain, the Aging Brain Initiative, and the newly-established Alana Down Syndrome Center. Research organized by and through these efforts and others is progressing rapidly. Indeed, many BCS faculty members, employing a variety of cutting-edge tools and techniques, study mechanisms that are currently thought to be most closely related to developmental disorders such as autism and dyslexia, to neuropsychiatric disorders such as schizophrenia and bipolar disorder, to neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease.

In this issue, you will read about Prof. Li-Huei Tsai's latest research that has revealed a new, potentially non-invasive avenue to treat Alzheimer's disease (page 3). Our cover story (page 4) does a deep dive into four of the many BCS faculty members working directly on how brain mechanisms can go awry. From where I sit, all of these amazing efforts and those of our entire community have one key thing in common — they each aim to build a scientific understanding of the mechanisms that underlie the mind. That scientific understanding will in turn lead to the emergence of entirely novel, rationally designed, highly effective ways to detect and ameliorate disorders of the human mind.

Though many questions about the brain and mind are left to answer, one thing is certain: we will not succeed in our mission without the hard work and dedication of our amazing community. From our faculty leading the charge in the labs, to the tireless efforts of our students, postdocs, research and administrative staff who do the work day-to-day; to the friends of the Department who provide the resources and support we need to keep going (page 14) — you are all vital to our mission. Each and every day, seeing your faces in the labs, hallways and classrooms reminds me of how lucky I am to be a part of this one of a kind community.

James J. DiCarlo, MD, PhD
Peter de Florez Professor of Neuroscience
Head, MIT Department of Brain & Cognitive Sciences

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Brain Wave Stimulation May Improve Alzheimer's Symptoms

Noninvasive treatment improves memory and reduces amyloid plaques in mice.

By Anne Trafton | MIT News Office

By exposing mice to a unique combination of light and sound, MIT neuroscientists have shown that they can improve cognitive and memory impairments similar to those seen in Alzheimer's patients.

This noninvasive treatment, which works by inducing brain waves known as gamma oscillations, also greatly reduced the number of amyloid plaques found in the brains of these mice. Plaques were cleared in large swaths of the brain, including areas critical for cognitive functions such as learning and memory.

"When we combine visual and auditory stimulation for a week, we see the engagement of the prefrontal cortex and a very dramatic reduction of amyloid," says Li-Huei Tsai, director of MIT's Picower Institute for Learning and Memory and the senior author of the study.

Further study will be needed, she says, to determine if this type of treatment will work in human patients. The researchers have already performed some preliminary safety tests of this type of stimulation in healthy human subjects.

MIT graduate student Anthony Martorell and Georgia Tech graduate student Abigail Paulson are the lead authors of the study, which appears in the March 14 issue of *Cell*.

Memory improvement

The brain's neurons generate electrical signals that synchronize to form brain waves in several different frequency ranges. Previous studies have suggested that Alzheimer's patients have impairments of their gamma-frequency oscillations, which range from 25 to 80 hertz (cycles per second) and are believed to contribute to brain functions such as attention, perception, and memory.

In 2016, Tsai and her colleagues first reported the beneficial effects of restoring gamma oscillations in the brains of mice that are genetically predisposed to develop Alzheimer's symptoms. In that study, the researchers used light flickering at 40 hertz, delivered for one hour a day. They found that this treatment reduced levels of beta amyloid plaques and another Alzheimer's-related pathogenic marker, phosphorylated tau protein. The treatment also stimulated the activity of debris-clearing immune cells known as microglia.

In that study, the improvements generated by flickering light were limited to the visual cortex. In their new study, the researchers set out to explore whether they could reach other brain regions, such as those needed for learning and memory, using sound stimuli. They found that exposure to one hour of 40-hertz tones per day, for seven days, dramatically reduced the amount of beta amyloid in the auditory cortex (which processes sound) as well as the hippocampus, a key memory site that is located near the auditory cortex.

"What we have demonstrated here is that we can use a totally different sensory modality to induce gamma oscillations in the brain. And secondly, this auditory-stimulation-induced gamma can reduce amyloid and Tau pathology in not just the sensory cortex but also in the hippocampus," says Tsai, who is a founding member of MIT's Aging Brain Initiative.

The researchers also tested the effect of auditory stimulation on the mice's cognitive abilities. They found that after one week of treatment, the mice performed much better when navigating a maze requiring them to remember key landmarks. They were also better able to recognize objects they had previously encountered.

They also found that auditory treatment induced changes in not only microglia, but also the blood vessels, possibly facilitating the clearance of amyloid.

Dramatic effect

The researchers then decided to try combining the visual and auditory stimulation, and to their surprise, they found that this dual treatment had an even greater effect than either one alone. Amyloid plaques were reduced throughout a much greater portion of the brain, including the prefrontal cortex, where higher cognitive functions take place. The microglia response was also much stronger.

"These microglia just pile on top of one another around the plaques," Tsai says. "It's very dramatic."

By exposing mice to a unique combination of light and sound, Tsai and her colleagues have shown that they can improve cognitive and memory impairments similar to those seen in Alzheimer's patients. At left, the mouse cortex shows a reduction in amyloid plaques following visual and auditory stimulation, compared to the untreated mouse at right. Image credit: Gabrielle Drummond

The researchers found that if they treated the mice for one week, then waited another week to perform the tests, many of the positive effects had faded, suggesting that the treatment would need to be given continually to maintain the benefits.

In an ongoing study, the researchers are now analyzing how gamma oscillations affect specific brain cell types, in hopes of discovering the molecular mechanisms behind the phenomena they have observed. Tsai says she also hopes to explore why the specific frequency they use, 40 hertz, has such a profound impact.

The combined visual and auditory treatment has already been tested in healthy volunteers, to assess its safety, and the researchers are now beginning to enroll patients with early-stage Alzheimer's to study its possible effects on the disease.

"Though there are important differences among species, there is reason to be optimistic that these methods can provide useful interventions for humans," says Nancy Kopell, a professor of mathematics and statistics at Boston University, who was not involved in the research. "This paper and related studies have the potential for huge clinical impact in Alzheimer's disease and others involving brain inflammation."

The research was funded, in part, by the Robert and Renee Belfer Family Foundation, the Halis Family Foundation, the JPB Foundation, the National Institutes of Health, and the MIT Aging Brain Initiative. ■

This article was originally published on MIT News.

Demystifying Disorder

BCS faculty use state-of-the-art tools and techniques to unravel the mysteries of the brain in health and in disorder.

By Sara Cody
BCS Communications

The human brain is a vastly complex system. While advances in tools and technologies to measure, probe, and analyze brain function have helped scientists uncover many mysteries about the brain, there is a lot we still do not know about the brain in health, much less in disorder. The stakes are high — the World Health Organization estimates that globally, about a billion people are impacted by brain disorders in some way — ranging from neurological disorders (like Alzheimer's or Parkinson's disease), to psychiatric disorders (like bipolar disorder) to developmental disorders (like autism or ADHD).

In the Department of Brain and Cognitive Sciences at MIT, researchers develop and employ a variety of state-of-the-art tools and techniques — including functional magnetic resonance imaging (fMRI), genetically engineered animal models enabled by CRISPR, and cell type-specific transcriptional profiling, to study the brain and all of its components. The key to unlocking the mystery behind any brain disorder could be hidden on any level — from the activity patterns in the whole brain to the molecules by which brain cells communicate with each other, to the genes that are responsible for producing the proteins that run everything in the brain.

This idea has crystallized into the core mission of BCS: to reverse engineer the mechanisms of the mind. Understanding what goes awry across all levels in the brain and developing and refining computational models to emulate these processes is critical to the discovery of new treatments and development of new preventative measures for disorders of the brain and mind.

Peering into the Whole Brain

Donning blue hospital scrubs, a volunteer lays back on the table as she listens to instructions from the researcher. The table is perched on the edge of the circular opening of a 3T magnetic resonance imaging machine (MRI) in the Martinos Imaging Center, housed in the lowest floor of the McGovern Institute for Brain Research (MIBR). The scanner contains a magnet that is 300 times stronger than the ones stuck to your kitchen refrigerator — no metal, not even a hair pin is allowed into the room containing the scanner. The volunteer, laying perfectly still on the table, is slowly moved into the enormous machine, which hums to life, whirring and clicking as the study begins. On the opposite side of a glass window researchers watch as the volunteer's entire brain unfurls in transections, pixel by pixel, on the monitor in front of them.

fMRI is a powerful imaging technique that measures brain activity through changes in blood flow and oxygen levels. Once inside the machine, volunteers perform a variety of tasks in the scanner — often involving language, emotion and memory — which researchers use to identify brains regions and activation patterns involved in different cognitive processes. Professor John Gabrieli uses fMRI, along with various behavioral measures, to study diversity in brain function and development, including in individuals with learning disabilities like dyslexia and developmental disorders like attention deficit hyperactivity disorder (ADHD) and autism.

"As imaging became a more practical tool, I was struck by idea that we could now look at how the brain develops differentially in children, which had been impossible to look at in our current population of adults with brain injuries," says Gabrieli, the Grover Hermann Professor of Health Sciences and Technology and Cognitive Neuroscience, an investigator in MIBR, Director of the Martinos Imaging Center and Director, MIT Integrated Learning Initiative. "The chance to look directly at a five-year-old's brain to learn more about how it grows, how it operates and how those processes relate to doing better or worse in school, or being better or worse emotionally seemed like a really interesting opportunity for research."

When Gabrieli was a graduate student, imaging techniques like fMRI were not widely available. Instead, researchers who wanted to understand brain differences were limited to working with adult patients with brain injuries or Alzheimer's disease. That changed when fMRI was made accessible. Today, Gabrieli's lab also considers the role of socioeconomic factors and environmental factors, such as early intervention and educational support, that may impact access to treatment and the presentation of developmental disorders. Taken together, Gabrieli's goal is to combine the basic science understanding of developmental disorders and the real-world social impacts to inform and improve practices and policies in education.

The ability to peer inside a live brain in a minimally invasive way has enabled key breakthroughs in our understanding of the neurobiology of developmental disorders and how they are impacted by environmental and social factors. For example, Gabrieli uncovered key brain differences in children who struggled with reading.

"There was a measurable difference in children even before getting reading instruction in school," says Gabrieli. "This was a key insight for us because it showed that we could identify children at high risk of struggling to read before they fail and initiate an intervention much earlier to provide additional support. It made us realize we were on the right path."

In a study using fMRI, Gabrieli and his research team discovered that in people with dyslexia, the brain has a diminished ability to acclimate to a repeated input — a trait known as neural adaptation. For example, when dyslexic students see the same word repeatedly, brain regions involved in reading do not show the same adaptation seen in typical readers. Throughout the series of experiments, Gabrieli and his team found that in people with dyslexia, brain regions devoted to interpreting words, objects, and faces, respectively, did not show neural adaptation when the same stimuli were repeated multiple times, which was surprising because people with dyslexia typically have no documented difficulty with recognizing objects and faces. This led Gabrieli to hypothesize that the impairment shows up primarily in reading because deciphering letters and mapping them to sounds is such a demanding cognitive task.

Being able to peer inside the whole brain enables Gabrieli to assemble the disparate pieces of the puzzle together, which vary greatly between individuals, in order to obtain a more complete picture of brain disorders.

• Prof. John Gabrieli
Photo credit Justin Knight, MIBR

Continued on next page

• Using fMRI, Gabrieli and his research team uncovered key brain differences in children who struggled with reading.

Closing the Gap

• Prof. Guoping Feng, Photo credit: Justin Knight, MIBR

Bringing new therapies from bench to bedside is a big challenge. Treatments can have promising results in lab mice but fail when tested in human patients. After attending medical school, Professor Guoping Feng, James W. (1963) and Patricia T. Poitras Professor and an MIBR investigator, initially pursued graduate school in pharmacology, where he hoped to develop treatments that would have a positive impact on the pediatric patients he saw in medical school. However, he quickly realized that huge gaps in our basic understanding of disease significantly impeded the development of new treatments.

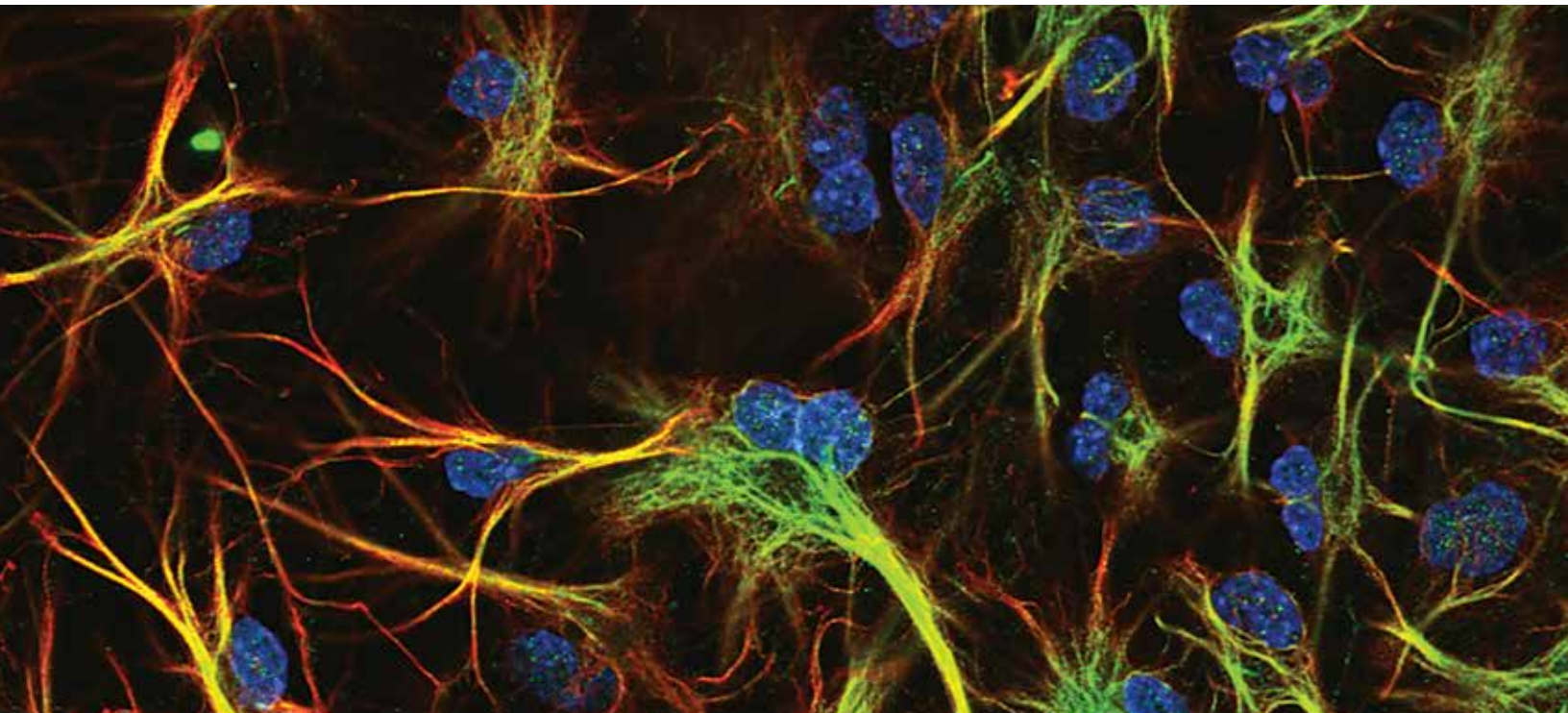
"I began to realize that without understanding the basic biology of disease, we will never develop a treatment for it," says Feng. "So I became more and more of a basic biologist and I did my PhD on nervous system development of fruit flies. I was drawn to molecular genetics because you could actually pinpoint the causes of a problem, which helps you solve it."

To better focus on human diseases, Feng switched from studying fly models to genetic mouse models for his postdoctoral studies — at the time the mouse was the only mammalian model available for genetic engineering. Today, Feng's research focuses on the development and function of synapses, and their disruption in neurodevelopmental and neuropsychiatric disorders. He uses molecular genetics combined with behavioral and electrophysiological methods to study the molecular components of the synapse and how disruptions in these components can lead to brain disorders.

One of Feng's first big breakthroughs involved a mouse model with a deleted scaffolding protein, Shank3, which is critical for brain development and implicated in autism spectrum disorder (ASD). While ASD has diverse genetic causes, most of which are still unknown, about one percent of people with autism are missing the Shank3 gene. Without this gene, individuals develop intellectual disability along with autism symptoms including repetitive behavior and avoidance of social interactions. The Shank3 protein is found at synapses — the connections that allow neurons to communicate with each other—where it helps to organize the hundreds of other proteins that are necessary to coordinate a neuron's response to incoming signals. Using CRISPR to precisely delete the gene, Feng's group found that these mutant mice exhibit autistic-like behaviors such as compulsivity, repetition of behavior and decreased social interaction, and showed that this gene produced these abnormal behaviors by interfering with communication between brain cells.

While these studies in mouse models provided helpful insight that can help pinpoint more targeted treatments for brain disorders, rodent brains are fundamentally different from primate brains, which limits the ability to translate discoveries into treatments for humans. CRISPR has made it possible to test human genetic mutations in non-human primates, which has enabled Feng and his research group to quantify and track the implications of Shank3 mutations in marmosets, and how it impacts more complex cognitive processes like social communication and working memory.

"One of the key differences between a rodent brain and a human brain is the expanded prefrontal cortex in the human brain, which is a major area controlling our decision-making, our emotions and our higher cognitive function. These structural differences produce vastly different behavioral outputs in the phenotypic expressions of these disorders and this may have contributed to the failures we have seen in translating this work to the clinic," says Feng. "So far, we have seen success in generating marmoset genetic models for brain disorders, whose brain structure and behavior are more similar to that of a human. We hope these new models will bring us much closer to new strategies for treatment."



• Researchers in Guoping Feng's lab have stained neurons in the mouse brain to reveal a protein related to autism and other brain disorders. Image: Michael Wells and Guoping Feng

The Power of Connection

Throughout life the brain can constantly adapt to a changing environment and in response to new experiences. This phenomenon called plasticity is implemented at the level of individual connections between brain cells (neurons). Neurons communicate with each other via neurotransmitter molecules released at connection points called synapses. Synapses can form and change strength during growth and development, but also prompted by a variety of factors including environment, injury, and activities like learning and reading. Professor Elly Nedivi, William R. (1964) & Linda R. Young Professor of Neuroscience and PILM investigator, studies the cellular mechanisms that underlie activity-dependent plasticity in the developing and adult brain.

"We are interested in plasticity, or the ability of the brain to adapt. The concept is similar to working out at the gym to make your muscles stronger or practicing something over and over so you can remember it better," says Nedivi. "You can take the same idea and apply it to individual connections in your brain. When we say these connections get stronger when they're used, what does that actually mean? How are the properties of the connections actually changing?"

By employing molecular and genetic techniques to study the dynamics of neuronal structure and identify the participating genes and the proteins they encode, what started as a question about the biology of this phenomenon led to new and exciting insights that could impact the way we understand and treat patients with bipolar disorder (BPD), an inheritable mood disorder characterized by recurrent episodes of high and low moods, or mania and depression. Left untreated, BPD worsens in patients, and researchers estimate that between 25 to 60 percent of BPD patients will attempt suicide at least once in their lives.

While conducting studies on the fundamental properties of synaptic plasticity, Nedivi discovered CPG2, a protein expressed in response to neural activity, that helps regulate the number of receptors for a key neurotransmitter, glutamate, at excitatory synapses. Regulation of glutamate receptor numbers is a key mechanism for modulating the strength of connections in brain circuits. When genetic studies identified SYNE1, the gene encoding CPG2, as a risk gene specific to BPD, Nedivi and her research team saw an opportunity to understand how a set of genetic differences in patients with bipolar disorder can lead to specific dysfunction of synapses in the brain.

"The levels of glutamate in the synapse contribute to the strength of the synapse itself, and pushing receptors for glutamate in and out of the synapse is a highly regulated process because it changes the sensitivity of the synapse to the transmitter," says Nedivi. The researchers are suggesting that the CPG2-related variations in SYNE1 likely contribute to susceptibility to bipolar disorder. Notably, they found that some human genetic variants found in bipolar patients, and in particular combinations of variants, could results in diminished CPG2 levels, and synaptic dysfunction.

"Our results align with the heritability of the disease where we know that there is a genetic element to a lot of neuropsychiatric disorders, and the genetic environment also impacts how different alleles get combined, which affects whether or not BPD emerges," says Nedivi, "In the lab, we can actually knock down the mouse or rat gene and replace it with the human gene and the model acts like it's at home, so it's a really helpful model for testing the impact of human mutations in vivo."

• Prof. Elly Nedivi
Photo credit: Josh Sariñana, PILM

For BPD patients, drug treatment requires a lot of trial and error and as a result, is often unsuccessful. In many cases, full recovery between episodes is not achieved in all patients. Models of BPD, like the ones developed in Nedivi's lab, not only shed light onto the mechanistic details of disease-related genetic mutations, but also offer an opportunity to study ways to prevent, manage, or even reverse the disease.

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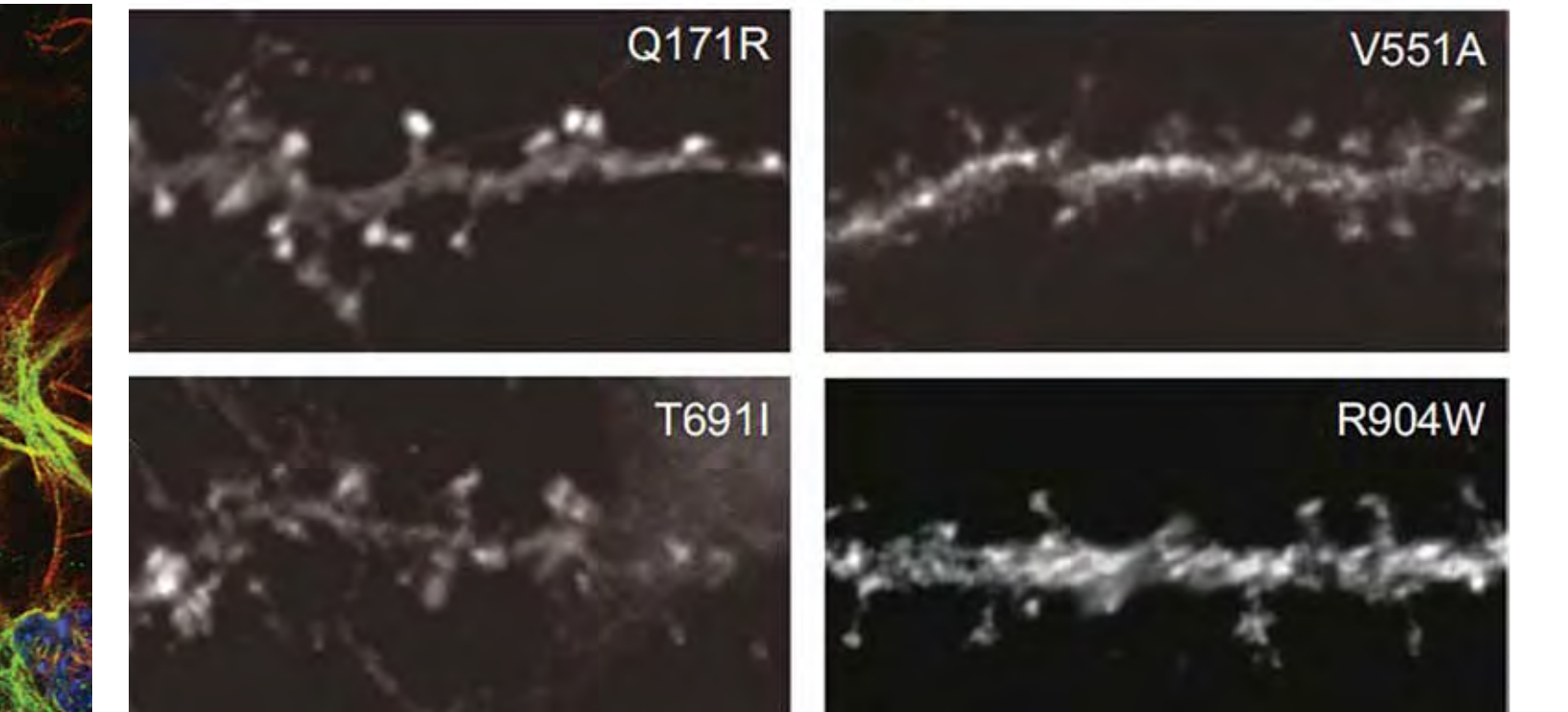


• Some variants of the SYNE1 gene, such as V551A top right, reduced the ability of the protein CPG2, shown here as bright spots, to locate in protruding spines of dendrites that house excitatory synapses in the neurons of rats. Image credit: Nedivi Lab/Picower Institute

• Prof. Myriam Heiman, Photo credit: Josh Sariñana, PILM

The brain is comprised of many different cell types including neurons, astrocytes, microglia, and oligodendrocytes, and many variations in the types of neurons and glia. Different disorders are not only specific to particular brain regions, but often to specific cell types. However, it has been difficult to characterize the function of cellular subtypes and pinpoint the mechanisms of dysfunction that underlie disorders.

Professor Myriam Heiman, Latham Career Development Chair and member of PILM, came to MIT armed with an expertise in cellular and molecular biology and a unique methodology she devised during her postdoctoral studies. TRAP or "Translating Ribosome Affinity Purification", enables cell type-specific transcriptional profiling to identify the pattern of protein production ongoing in a particular cell type. Heiman uses a combination of TRAP and genetic screening methods to study the underlying mechanisms of degenerative diseases in the central nervous system, which includes Huntington's disease and Parkinson's disease.

"Though these diseases have distinct clinical presentations, they are both caused by dysfunction of the basal ganglia in the brain, which is a group of subcortical areas that are important in many developmental and degenerative diseases," says Heiman. "Our approach is first to understand how these neurons work in a normal developmental situation, and then to understand how they dysfunction in disease states."

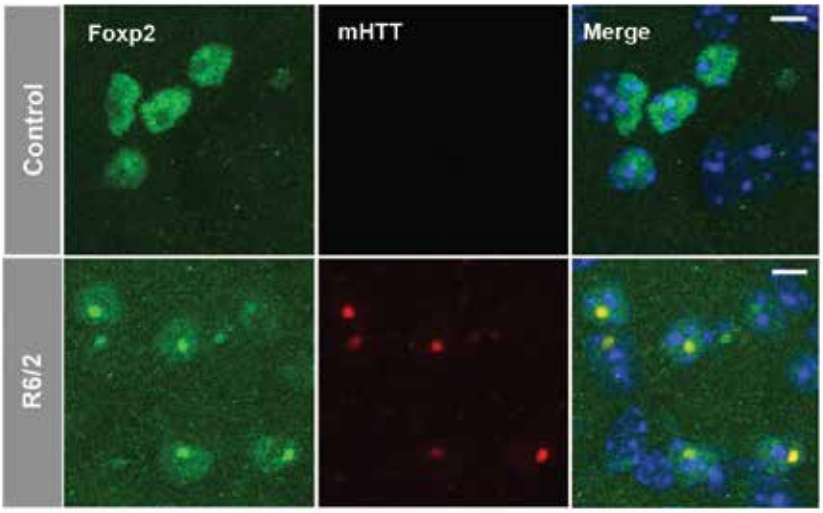
Huntington's disease is a genetic, progressive, neurodegenerative disorder characterized by gradual, involuntary muscle movements and progressive deterioration of cognitive processes and memory (i.e. dementia). In Huntington's disease, a specific subtype of neuron, striatal spiny projection neurons (SPNs), are especially vulnerable to the genetic defect underlying the disease, and this enhanced vulnerability is also seen in animal models of the disease. Heiman utilized her TRAP method to understand the mechanisms behind this vulnerability. One of her first key findings with the enhanced resolution that TRAP offers is that the genetic defect in HD caused an alteration to transcription in SPNs during very early stages of the disease model. Previously, it hadn't been known whether this transcriptional dysregulation was a cause or consequence of the disease taking hold, but it was a clear indication from the early timing that this represented a first step involved in the eventual death of these particular neurons.

This finding led to Myriam identifying Foxp2, an important gene in the basal ganglia that is connected to producing and comprehending speech. Heiman noticed that Foxp2 has a section of its gene encoding many glutamine amino acids in a row, a region called a polyglutamine domain. Other researchers had previously found that the mutant HD gene also has an expanded polyglutamine domain in the disease state, and it can cause other polyglutamine-containing proteins to lose function. Seeing the parallel in the Foxp2 made Heiman question whether there was a connection between the two.

"From pioneering work by Ann Graybiel and others, we know that Foxp2 also has a more primitive role, in regulating how the cortex communicates with the striatum. We became interested in Foxp2, because in Huntington's disease, these communication points between the cortex and the striatum are thought to be among the first part of the neurons that dysfunction in HD," says Heiman. "It is likely that Foxp2 is also important in the maintenance of these communication points, or synapses, after they form. Further, we noticed that Foxp2 has a polyglutamine domain, a stretch of many glutamine amino acids in a row, similar to the polyglutamine domain that is expanded in the Huntingtin gene in HD. Could it be that the mutated gene is basically sticking onto Foxp2 and preventing it from doing its job and impeding proper neural communication?"

To test this idea, Heiman first decreased levels of Foxp2 in mouse models and observed HD-associated changes in behavior relevant to HD. When Heiman added the protein back into two of the HD mouse models for the second part of the experiment, she observed a surprising phenomenon: the HD-associated deficits in the mice from removing Foxp2 decreased.

"From our findings, we think that Foxp2 protein interacts with the HD gene protein through their polyglutamine domains. Our paper concluded that given these two proteins are in the same place physically in the cell, we think part of the early deficits seen in HD may be attributable to the lack of proper Foxp2 function," says Heiman. "Because transcription factors control many genes, they are incredibly difficult to work with in human gene therapy, but it certainly presents an opportunity to see if we can restore the effects of Foxp2 function in potential future therapies." ■



• The above image compares the control mouse striatal tissue (top row) with striatal tissue from a transgenic mouse with an HD gene mutation (bottom row) that mimics features of HD. The first column shows the Foxp2 protein, the second column shows the mutant Huntingtin protein, and the third column shows both Foxp2 and mutant Huntingtin together. The R6/2 merge (bottom right) shows Foxp2 and mutant Huntingtin are co-localized in the striatal tissue, supporting the hypothesis that the interaction between the two may be implicated in Huntington's disease. Image courtesy of the researchers

Stories by Anne Trafton and David Orenstein contributed to this report. View the full stories online at ***bcs.mit.edu***

Research Bytes

Here is a snapshot of the latest discoveries from BCS faculty and their research teams. To read the stories in full and to get the latest research news, **visit bcs.mit.edu**.

Teaching machines to reason about what they see

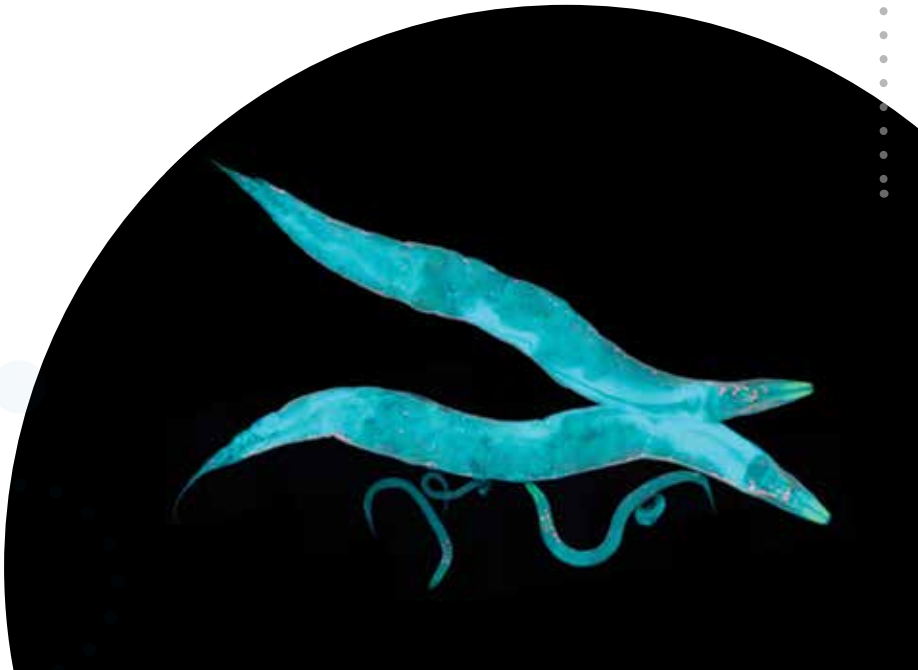
Deep learning systems interpret the world by picking out statistical patterns in data. This form of machine learning is now everywhere, automatically tagging friends on Facebook, narrating Alexa's latest weather forecast, and delivering fun facts via Google search. But statistical learning has its limits. It requires tons of data, has trouble explaining its decisions, and is terrible at applying past knowledge to new situations. To give computers the ability to reason more like us, artificial intelligence (AI) researchers are returning to abstract, or symbolic, programming. A study by a team of researchers at MIT, MIT-IBM Watson AI Lab, and DeepMind shows the promise of merging statistical and symbolic AI. Led by postdoc Jiajun Wu and Prof. Joshua Tenenbaum (BCS/CSAIL/CBMM/Quest), the team shows that its hybrid model can learn object-related concepts like color and shape, and leverage that knowledge to interpret complex object relationships in a scene. With minimal training data and no explicit programming, their model could transfer concepts to larger scenes and answer increasingly tricky questions as well as or better than its state-of-the-art peers.

— Kim Martineau | MIT Quest for Intelligence

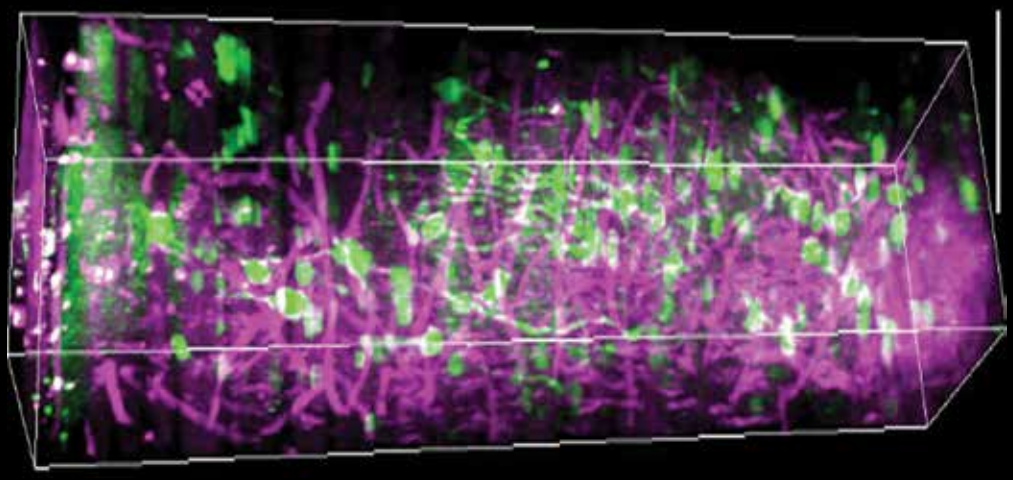
Gut-brain connection signals worms to alter behavior while eating

When a hungry worm encounters a rich food source, it immediately slows down so it can devour the feast. Once the worm is full, or the food runs out, it will begin roaming again. In all animals, the gut and the brain have a strong connection. Signals from our gastrointestinal tract let us know when we're full and help to control our appetite, via hormones such as leptin and ghrelin. The GI tract is also the source of most of the body's serotonin, which also play a role in appetite. A study led by Prof. Steven Flavell (PILM) found that a type of nerve cell, serotonin-producing enteric neurons called neurosecretory-motor (NSM) neurons, found in the gut of the worm *Caenorhabditis elegans*, is specialized to detect when bacteria are ingested; once that occurs, the neurons release a neurotransmitter that signals the brain to halt locomotion. The researchers also identified new ion channels that operate in this specialized nerve cell to detect bacteria, the main food source of *C. elegans*. This study provides insight on the mechanisms of how food ingestion is detected by the nervous system to drive a behavioral change.

— Anne Trafton | MIT News Office



Researchers found that a type of nerve cell found in the gut of the worm *Caenorhabditis elegans* is specialized to detect when bacteria are ingested.



A 3-D rendering of mouse visual cortex stretching from the surface at left to the subplate on the right. The green color represents calcium signals of neural activity and magenta represents blood vessels and myelin fibers in the white matter. Image credit: Sur Lab

Scope advance gives first look through all cortical layers of the awake brain

By substantially refining the three-photon microscopy technique, Prof. Mriganka Sur, (PILM/Director, Simons Center for the Social Brain) conducted the first-ever study of stimulated neural activity in an awake mouse through every visual cortex layer and notably the mysterious subplate below. The team showed that as mice watched visual stimuli, their human observers could measure patterns of activity among neurons in all six layers of visual cortex and the subplate, providing new data about their role in how mammals process vision. Moreover, through a series of careful experiments, the researchers were able to show that the light they sent in, as well as the light that came back out, neither damaged, nor even altered, the cells they measured. In all, the paper describes a new three-photon microscope optimized to deliver rapid, short, low-power pulses of light capable of reaching deep targets without causing any functional disturbance or physical damage, and then to detect the resulting fluorescence emitted by cells with high efficiency to produce images with sharp resolution and a fast frame rate. This new technique addresses previous challenges associated with imaging subplate neurons in a mature adult brain in vivo.

— David Orenstein | Picower Institute for Learning and Memory

Scientists engineer new CRISPR platform for DNA targeting

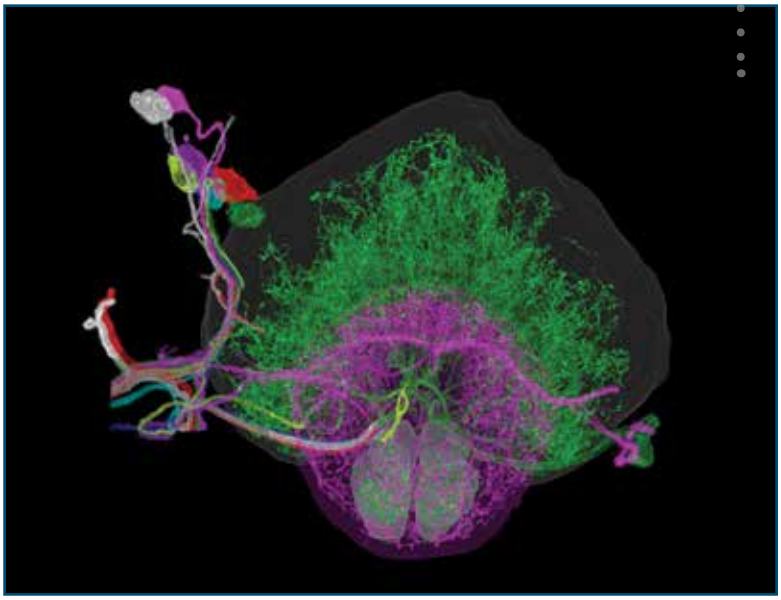
Prof. Feng Zhang (MIBR/Broad) and colleagues at the Broad Institute of MIT and Harvard, MIBR, and the National Institutes of Health engineered another CRISPR system, called Cas12b. The new system offers improved capabilities and options when compared to CRISPR-Cas9 systems. demonstrate that the new enzyme can be engineered to target and precisely nick or edit the genomes of human cells. The high target specificity and small size of Cas12b from Bacillus hisashii (BhCas12b) as compared to Cas9 (SpCas9), makes this new system suitable for in vivo applications. The team is now making CRISPR-Cas12b widely available for research.

— The Broad Institute of MIT and Harvard

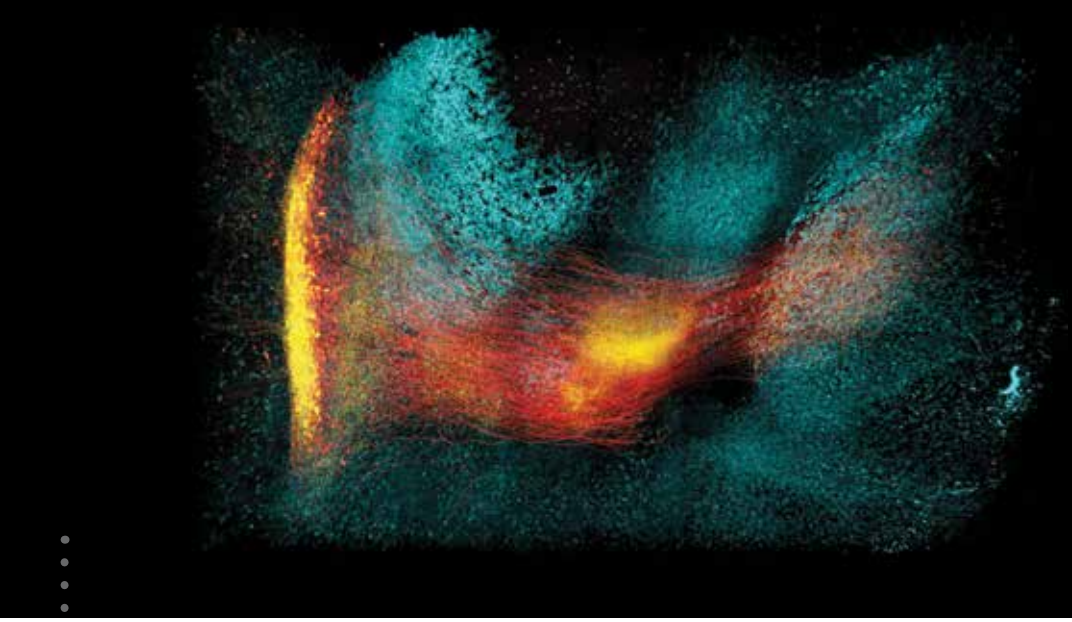
Mapping the brain at high resolution

Researchers have developed a new way to image the brain with unprecedented resolution and speed. Using this approach, they can locate individual neurons, trace connections between them, and visualize organelles inside neurons, over large volumes of brain tissue. The new technology combines a method for expanding brain tissue, making it possible to image at higher resolution, with a rapid 3-D microscopy technique known as lattice light-sheet microscopy. The researchers, led by Prof. Ed. Boyden (MIBR/BE/Media Lab), showed that they could use these techniques to image the entire fruit fly brain, as well as large sections of the mouse brain, much faster than has previously been possible. The team includes researchers from MIT, the University of California at Berkeley, the Howard Hughes Medical Institute, and Harvard Medical School/Boston Children's Hospital. This technique allows researchers to map large-scale circuits within the brain while also offering unique insight into individual neurons' functions.

— Anne Trafton | MIT News



Individually traced dopaminergic neurons in theright hemisphere of a fruit fly brain, innervating the fan-shaped body (green), ellipsoid body (magenta), and noduli (green). Image courtesy of the researchers.



MIT researchers used their new tissue preservation technique to label and image neurons in a brain region called the globus pallidus externa. Neurons that express a protein called parvalbumin are labeled in red, and neurons labeled blue express a protein called GAD1. Image credit: Young-Gyun Park, Changho Sohn, Ritchie Chen, and Kwanghun Chung

Mapping the brain, cell by cell

Prof. Kwanghun Chung (BCS/PILM/ChemE/IMES) and his research team have devised a new way to preserve biological tissue, allowing them to visualize proteins, DNA, and other molecules within cells, and to map the connections between neurons. They showed that they could use this method, known as SHIELD, to trace the connections between neurons in a part of the brain that helps control movement and other neurons throughout the brain. Once the tissue is preserved, the researchers can label a variety of different targets, including proteins and mRNA produced by the cells. They can also apply techniques such as MAP, which Chung developed in 2016, to expand the tissue and image it at different size scales. The speed of SHIELD tissue processing means that it also holds promise for performing rapid, more informative biopsies of patient tissue samples. Chung is now leading a team of researchers from Massachusetts General Hospital, Princeton and the MIT Lincoln lab that recently received a National Institutes of Health grant to use this technique to produce three-dimensional maps of the entire human brain.

— Anne Trafton | MIT News Office

How the brain distinguishes between objects

As visual information flows into the brain through the retina, the visual cortex transforms the sensory input into coherent perceptions. Neuroscientists have long hypothesized that a part of the visual cortex called the inferotemporal (IT) cortex is necessary for the key task of recognizing individual objects, but the evidence has been inconclusive. A study published by Prof. James DiCarlo (MIBR/CBMM/Quest) found clear evidence that the IT cortex is indeed required for object recognition; they also found that subsets of this region are responsible for distinguishing different objects. In addition, the research team, led by Rishi Rajalingham, developed computational models that describe how these neurons transform visual input into a mental representation of an object. They hope such models will eventually help guide the development of brain-machine interfaces (BMIs) that could be used for applications such as generating images in the mind of a blind person. The research was funded by the National Eye Institute, the Office of Naval Research, and the Simons Foundation.

— Anne Trafton | MIT News Office

What's in a face?

In a recent study, Prof. Nancy Kanwisher (MIBR/CBMM) and her research team measured the response of the brain to faces in real-time, and found that the brain first decodes properties such as gender and age before drilling down to the specific identity of the face itself. Using magnetoencephalography (MEG), a technique developed by MIT physicist David Cohen that detects the minuscule fluctuations in magnetic fields that occur with the electrical activity of neurons and allowing for better temporal resolution of neural activity, the researchers measured the time it takes for the brain to respond to different dimensional features of faces. They found that the brain responds to coarse features, such as the gender of a face, much faster than the identity of the face itself, suggesting that the brain may be remembering associations related to the face in that longer timeframe. This insight has potential implications for artificial intelligence and whether feed-forward deep learning systems can learn faces using similar mechanisms.

— Sabbi Lall | McGovern Institute for Brain Research ■

In Her Own Words:
Ashti Shah'20

As told to Sara Cody | BCS Communications

How far can I push myself? For me, the only place I could answer this question is at MIT, which helped me decide to come here initially. Medical school has always been on the horizon for me, so I knew I wanted to pursue a major in the life sciences, but after being exposed to a broad range of classes in different subjects my first year, I know I wanted to continue to do a little bit of everything. That's how I ultimately landed in Course 9–it's so interdisciplinary. You can take classes in cellular/molecular science, lab skills, computation and more just within BCS, and I have continued to enjoy the ability to take classes in other departments at MIT too.

My first UROP experience led me to Prof. John Gabrieli's lab after taking his 9.00 class, where I worked under the mentorship of postdoctoral fellow Nicholas Hubbard to learn the ropes of working in a lab, navigate my own understanding of the research, and eventually develop and conduct my own experiment. Research in the GabLab focuses on using brain imaging techniques and behavioral testing to understand how we learn, think and feel, how these factors differ across diverse populations and to use this information to help those with neurodevelopmental disorders. At first, I spent a lot of time reading papers and jumping in to help out on odd projects like data collection, writing data analysis scripts and other tasks.

For my own experiment, I used functional near infrared spectroscopy (fNIRS), a noninvasive imaging technique that measures brain activity through hemodynamic responses. Using electrodes, you can connect a human subject to the machine and observe changes in oxy- and deoxygenated hemoglobin levels in their brain to help you pinpoint where in the brain processes that particular behavior, task or activity. In adults, we have a rough timeline for working memory that grows in childhood, plateaus in adulthood and decays in old age. In my experiment, I looked at healthy adults to understand how individual differences affect the process of working memory in the brain. To our knowledge, no one had used fNIRS to study healthy adults using the kind of task paradigm we outlined in the experiment, and it provides a good baseline of data to eventually branch out into other patient populations to track how these variables impact working memory. Eventually, we hope to develop this technique even further to serve as a clinical tool in the future.

Coming to a world-renowned research institution like MIT, I wanted to make sure that I incorporated laboratory experience into my coursework, and I'm so glad I did. The Course 9 curriculum provides a strong foundation of the tools and skills you need to approach problems, and one of the most surprising things I have learned through my research experience is that everyone in the lab is actively learning, all of the time. It was a huge shift in perspective for me because as a student, you are primarily memorizing pre-existing knowledge, but in the lab, you are charting completely new territory, and that's what makes it really exciting. Even though it took eighteen months to get to this point, it's also exciting to be in the process of being able to explain my research succinctly and write up my own experimental results to submit for publication. As my project in the Gabrieli lab winds down, I recently joined Prof. Rebecca Saxe's lab and I can't wait to see where this new experience takes me! ■

Noteworthy News

Mark Bear received the 2018 Beckman-Argyros Vision Research Award from The Arnold and Mabel Beckman Foundation.

Steven Flavell received the NSF CAREER Award.

Elly Nedivi was named the inaugural William R. (1964) & Linda R. Young Professor of Neuroscience.

Li-Huei Tsai received The Hans Wigzell Research Foundation Science Prize for 2018 in recognition of her work "to understand the etiology and possible treatment of Alzheimer´s disease."

BCS undergraduates **Yotaro Sueoka** and **Lena Zhu** were among the 2019 class of Burchard Scholars selected by the MIT School of Humanities, Arts, and Social Sciences (SHASS). The program recognizes "promising sophomores and juniors who have demonstrated excellence in some aspect of the humanities, arts, or social sciences."

Feng Zhang was promoted to full professor.

Myriam Heiman, Mehrdad Jazayeri, and **Josh McDermott** were promoted to Associate Professor.

Ted Gibson was inducted into the MIT Quarter Century Club, which celebrates 25 years of employment at MIT.

Michael Halassa was appointed Max Planck Fellow by Max Planck Florida Institute for Neuroscience (MPFI).

The recipients of the Angus MacDonald Award for Excellence in Undergraduate Teaching by a Graduate Student included **Andres Crane, Junyi Chu, Mika Braginsky, Michael Lee, Chad Sauvola, Jonathan Gauthier, Maxwell Nye, Anna Ivanova, Jungsoo Kim** and **John Tauber**.

The recipients of the Walle Nauta Award for Excellence in Graduate Teaching by a Graduate Student were **Jenna Aronson** and **Nhat Le**.

The recipients of the Walle Nauta Award for Continuing Dedication to Teaching by a Graduate Student included **Scarlett Barker, Madeline Pelz, Matthias Hofer** and **Luke Hewitt**.

Congratulations to **Martha Constantine-Paton** on her retirement!

Mark Harnett received the BCS Award for Excellence in Undergraduate Advising.

Laura Schulz received the BCS Award for Excellence in Undergraduate Teaching.

Steven Flavell received the BCS Award for Excellence in Graduate Mentoring.

Mehrdad Jazayeri received the BCS Award for Excellence in Graduate Teaching.

Rebecca Saxe received the BCS Award for Excellence in Postdoctoral Mentoring.

Community Highlights

1. To celebrate Grad Student Appreciation Week, BCS hosted a donut wall, complete with a latte station. Thank you to our grad students for all of their hard work! (Left to right, **Malinda McPherson, Andrew Francl, Mahdi Ramadan, Madeline Pelz, Martin Schrimpf, Jarrod Hicks,** and **Peng Qian**). Photo credit: Matthew Regan
2. BCS Department Head **Jim DiCarlo** presented the 2018 BCS Teaching and Mentorship Awards at the 2019 Hans-Lukas Teuber Lecture. Graduate student recipients include (left to right) **Mattias Hofer, Nhat Le, Jenna Aronson, John Tauber, Jungsoo Kim, Anna Ivanova, Jon Gauthier, Michael Lee, Andres Crane,** and **Scarlett Barker**. Not pictured: **Junyi Chu, Mika Braginsky, Chad Sauvola and Luke Hewitt**.
3. 2018 faculty recipients of the BCS Teaching and Mentorship Award with BCS Department Head **Jim DiCarlo** include (left to right) **Mehrdad Jazayeri, Laura Schulz, Mark Harnett** and **Steve Flavell**. Not pictured: **Rebecca Saxe**.
4. **Matheus Victor**, postdoctoral associate in **Prof. Li-Huei Tsai**'s lab, was selected as a winner of the Koch Institute Image Awards. His research image, "Circuit Training: Shining a Light on Neural Development" is currently on display in the Koch Institute. The image depicts a synthetic brain circuit with engineered light-activated neurons (blue and white) that respond to stimulation patterns that mimic excitatory signals from the developing brain. The electrodes in the foreground record the transmission of signals between cells, revealing important information about the development of neural networks. Photo credit: Samara Vise ■

From the Rules of Order to a Better World

***William R.**'64 and **Linda Young** provide philanthropic support for MIT's Department of Brain and Cognitive Sciences*

By: Sara Cody | BCS Communications

William R.'64 and Linda R. Young. Image provided by the Young family

In the 1960s, personal photography exploded in popularity thanks to the invention of the Kodak Instamatic, an inexpensive, easy-to-use point-and-shoot camera. Suddenly, photography was accessible to everyone and it became a massive commercial success. The Eastman Kodak Company, headquartered in Rochester, N.Y, was in its heyday, and for William R. Young '64, growing up in a science town set him down a path that ultimately led him to MIT.

"Eastman Kodak was the biggest thing in town, and there were a lot of scientists and engineers, working at Kodak, who were part of our suburban community," says Mr. Young. "The whole place was steeped in science, and that rippled out to other areas, the schools in particular."

While attending a science seminar at school that was championed by local scientists, Young met one of the event sponsors, who happened to be an MIT alum. They struck up a friendship and Young was inspired to apply to MIT at the recommendation of his friend. When it came time to choose his undergraduate major at MIT, he chose chemistry, a decision that would shape his experience at MIT and eventually lead him to pursue his graduate degree at the University of California, Berkeley. He began his professional career as a research chemist at IBM Research, focusing on the development of novel liquid crystals that could be used in displays — a sector that was then in its infancy. While at IBM, he began his evening studies that ultimately led to receiving his MBA from Pace University.

"In any field, you have to have rules of order, and that is the defining feature of science and mathematics," says Mr. Young. "For me, transitioning to business was natural because there are many parallels between science and finance; each sector required an underlying set of fundamentals, such as conservation of mass and energy and net molecular neutrality in chemistry and rigorous accounting and the application of economic principles, such as supply and demand in finance. Given the assignment of such rules of order, I saw a clear need for companies to employ corporate leaders with the mindset to navigate within these tenets."

In chemistry, one of the universally-known rules of forming a strong chemical bond is "opposites attract." The same could be said of Young and his wife, Linda. Whereas Young had built his life around his interest in science, Linda, a psychology major from the University of Hartford, was passionate about art and music, having played the orchestral violin and sung in choirs for years. Their connection was immediate when they met at a mixer in 1968, and they built a strong foundation for their marriage of 50 years.

The Young family eventually settled in Greenwich, Conn. Young continued his career in the private sector rising to the role of Managing Director at Credit Suisse and earning the #1 Chemical Industry Analyst rank for 17 consecutive years by Institutional Investor magazine. Mrs. Young pursued a career in human resources — including a stint at Reader's Digest — and eventually became a real estate agent, all while keeping up with her musical hobbies.

The couple had two children, a daughter who is now a social activist and doula and a son who followed in Young's footsteps as an MIT alum who became a biomedical engineer. While life together unfolded, Young maintained his ties to MIT, serving as an alumnus Educational Counselor on behalf of the Admissions Department and interviewing prospective freshmen who were high school seniors. Eventually, the Youngs made the decision together that they wanted to support MIT even further in foundational research.

> *"We became interested in supporting (BCS) because we wanted to direct our resources to an **area of high need** with a **tremendous opportunity** to **impact society** over the near term..."*

"We became interested in supporting the Department of Brain and Cognitive Sciences at MIT because we wanted to direct our resources to an area of high need with a tremendous opportunity to impact society over the near term," says Mrs. Young. "For example, a lot of work and progress has been made in understanding autism, bipolar disorder, depression, schizophrenia and more, and given the number of families who are impacted by these diagnoses, we wanted to dedicate our efforts to help."

BCS, and its mission to reverse engineer the mechanisms of the mind, takes a holistic approach to studying the brain and how it gives rise to the mind. By studying the mechanical underpinnings of the behavioral phenomena that makes us human, the Department casts a wide net, and, for the Youngs, the focus on basic science accelerating transformative discoveries that could potentially impact society reflected the intersection of their interests.

During a visit to the MIT campus last summer, the Youngs had the opportunity to meet Prof. Elly Nedivi in her laboratory in the Picower Institute for Learning and Memory. Nedivi studies the cellular mechanisms that underlie activity-dependent plasticity — the brain's ability to constantly adapt to a changing environment and in response to new experiences in the developing and adult brain.

"Elly's focus on genetics and proteins and their basic underlying chemistry that affects the neuron is very relevant to my interest in foundational science. Her work in deciphering genetic expression of proteins and synapse growth, or lack thereof, is significantly bolstering our grasp of brain plasticity," says Mr. Young. "For a musician like Linda, learning how the brain changes and adapts as it learns a new song, for example, was fascinating too. For us, the brain is a natural extension of both of our interests."

Their visit to campus cemented their decision to support BCS, and they made a gift to endow the William R. (1964) & Linda R. Young Professor of Neuroscience, which will support a significant number of BCS faculty, in perpetuity. Nedivi was selected as the inaugural recipient of the professorship.

"Linda and I have been in this partnership for 50 years," says Mr. Young. "Making this decision to establish a professorship has been a very special experience for us to have together, and we are delighted to support the efforts within BCS." ■

Help us shape the future of brain and cognitive sciences research

- **Support our graduate students**
  Our department is only as strong as the talented young scientists we can attract and cultivate. Help us shape the future of the field. Those who support our graduate students with either expendable or endowed fellowships become part of the Champions of Brain Fellows program.

- **Support diversity**
  Our Research Scholars Program provides students from disadvantaged backgrounds the mentorship and training needed to apply to graduate school. Help diversify the pipeline of scientists!

- **Create a named chair for young faculty or tenured faculty**
  Named chairs are a wonderful way to recognize the immense contributions our faculty make to the field and impact the department for years to come

- **Start or endow a fund to seed research in an area of your choice**
  Transformative science often stems from original — and often risky — ideas. Not only is the federal funding climate uncertain, but federal funding mechanisms do not typically fund ambitious projects or early-stage ideas.

Founding Champion **Barrie Zesiger** (center) talks with 2018 Zesiger fellow **Mattias Hofer** (left), a third-year graduate student in Prof. Roger Levy's lab studying psycholinguistics and 2016 Zesiger Fellow **Tobias Kaiser** (right), a fifth-year graduate student in Prof. Guoping Feng's lab who is developing new gene therapy approaches to improve brain disorder outcomes. Photo credit: Steph Stephens

The human mind represents one of the last great frontiers of scientific exploration. Our research is making progress in understanding the brain in health and disease, advancing human and machine intelligence, transforming the science of education, and helping us better understand ourselves. We rely on the generosity and support of our philanthropic partners to empower our talented students, scientists, and faculty to pursue bold ideas and innovative, cutting-edge research that leads to groundbreaking discoveries.

For more information, please contact:
Rachel Donahue, PhD
Director of Strategic Scientific Development and Industry Relations, BCS
617.715.2898 | rjd@mit.edu

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Rachel Donahue, PhD
Director of Strategic
Scientific Development
and Industry Relations, BCS

617.715.2898 | rjd@mit.edu

Contact BCS

MIT Department of Brain and
Cognitive Sciences

77 Massachusetts Avenue, 46-2005
Cambridge, MA 02139

Bcs-info@mit.edu | 617.253.5748

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