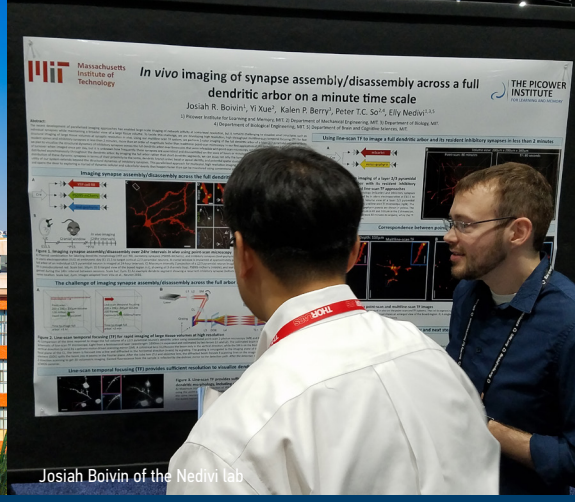


Josiah Boivin of the Nedivi lab

Picower at 'SfN'

Dozens of Picower scientists presented their latest research at the Society for Neuroscience Annual Meeting in San Diego **Pg. 8**

Littleton lab members Elizabeth Brija, Nicole Aponte Santiago and Monica Quiñones Frías. Image courtesy Aponte.

ALSO INSIDE

Neuroscience News

MIT WINTER 2018

THE PICOWER INSTITUTE FOR LEARNING AND MEMORY

DIRECTOR'S **MESSAGE**

Dear Friend,

Science is systematically social. We publish discoveries, reviewed by peers, to tell fellow scientists about them. We teach so that students can question and learn. We convene conferences and symposia to encourage discussion. In the lab we work in teams. Our job may sometimes require long hours at the bench, but progress wouldn't be possible if we didn't constantly engage conversations.

No event magnifies the socialness of our field more than the annual Society for Neuroscience conference. At "SfN" tens of thousands of neuroscientists mingle for nearly every purpose one can imagine, ranging from seeing old friends and making new ones to recruiting and job seeking, to discussing and debating research. With thousands of research posters and hundreds of talks, it's an extraordinary – sometimes overwhelming – exchange of ideas. Our cover story in this edition (page 8) summarizes our presence at SfN this year, illustrating some of the breadth of our research and also the many ways our scientists and students interface with the field.

Just a few weeks before SfN, we convened our own meeting, "Frontiers in Neurotechnology." Organized by Assistant Professor Kwanghun Chung, the Fall Symposium (p. 10) brought together 10 speakers and hundreds of attendees to discuss the latest advances in modeling, labeling and imaging the brain and its components to advance our understanding of how it develops, functions and is affected by disease. Kwanghun, who has developed many key technologies in this area, will now lead an exciting collaboration to make extraordinary maps of the entire human brain (p. 7).

Importantly, science's social circle encompasses more than just researchers. Philanthropists, for instance, are not only members of the neuroscience conversation, but in a real sense they are the conversation starters. On page 6 we tell the story of a new project that The Ludwig Family Foundation has helped my lab to launch.

Thank you for reading. We hope you enjoy hearing from us and taking part in our conversation, too.

LI-HUEI TSAI, DIRECTOR
Picower Institute for Learning and Memory

Image credit: Christine Daniloff

Dopamine Primes the Brain for Enhanced Vigilance

Picower Institute neuroscientists have discovered a circuit that appears to control the diversion of attention away from everyday pursuits to focus on potential threats. Dopamine is key to the process: It is released in the prefrontal cortex (PFC) when danger is perceived, stimulating the PFC to redirect its focus to a brain region that responds to threats.

When this circuit is off-balance, it could trigger anxious and paranoid behavior, possibly underlying some of the symptoms seen in schizophrenia, anxiety, and depression, said Associate Professor Kay Tye, senior author of the study published in *Nature*.

The lead authors are Caitlin Vander Weele, Cody Siciliano, and Gillian Matthews.

The team identified two neuron populations in the PFC. One population sends information to the nucleus accumbens, which is involved in motivation and reward, and the other relays information to the periaqueductal gray (PAG), in the brainstem. The PAG is involved in defensive behavior such as freezing or running.

Amid a threat, the ventral tegmental area sends dopamine to the PFC. Tye's team wanted to determine how dopamine affects the two populations. They designed an experiment where rats were trained to recognize two visual cues, one associated with sugar water and one with a mild electrical shock.

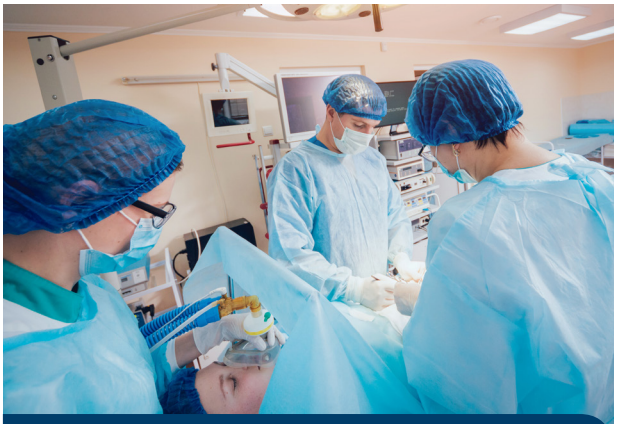
If they stimulated dopamine release when the cues were given simultaneously, the rats were much more likely to freeze (their normal response to the shock cue) than to pursue the sugar water. If they stimulated dopamine when just one of the cues was given, the rats' behavior was not affected. Dopamine appeared to enhance the escape response when the animals received conflicting information.

Further experiments suggested that dopamine acts by adjusting the signal-to-noise ratio in PFC neurons. When neurons that connect to the PAG receive dopamine at the same time as a threatening stimulus, their signal goes up and the noise decreases. Dopamine may activate other neurons that help to amplify the signals already coming into the PAG-connected neurons.

Dysregulation of this dopamine-controlled switching may contribute to neuropsychiatric disorders such as schizophrenia, Tye said. Among other effects, too much dopamine could lead the brain to weigh negative inputs too highly. This could result in paranoia, often seen in schizophrenia patients, or anxiety.

■ In **Nature:** *Dopamine enhances signal-to-noise ratio in cortical-brainstem encoding of aversive stimuli,* Nov. 7, 2018, http://bit.ly/Tye-dopa

Improving Anesthesia with Focus on Neuroscience, 'Nociception'



A new strategy for general anesthesia based on neuroscience could result in better care for patients.

Anesthesia is really four brain states — unconsciousness, amnesia, immobility, and suppression of the body's damage sensing response, or "nociception." In *Anesthesia and Analgesia*, Edward Hood Taplin Professor Emery N. Brown and colleagues argue that by putting nociception at the top of the priority list and taking a principled neuroscientific approach to choosing which drugs to administer, anesthesiologists can use far less medication overall, producing substantial postoperative benefits for patients.

"We've come up with strategies that allow us to dose the same drugs that are generally used but in different proportions that allow us to achieve an anesthetic state that is much more desirable," said Brown, a member of the Picower Institute and a practicing anesthesiologist.

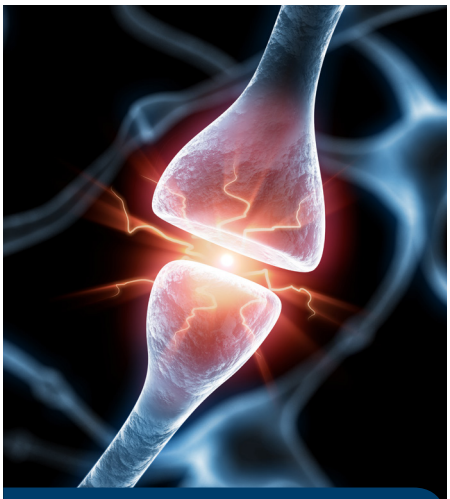
In the paper Brown and co-authors lay out exactly how and where each major anesthetic drug affects the nociceptive circuits of the nervous system. Nociception is the body's sensing of tissue damage. It is not pain, which is a conscious perception of that.

Then the authors show how in four different surgical cases they were able to use neuroscience to guide their choice of a "multimodal" combination of drugs to target nociceptive circuits at several different points. That way they didn't have to use much of any individual drug including opioids. Because reduced arousal is a byproduct of the strategy, they also didn't have to administer much medicine to ensure unconsciousness, a state they monitor by watching brainwaves captured by electroencephalography. Brown would like more colleagues to do this.

"If you do it this way, you have better control of nociception and you can get the same amount of unconsciousness with less drug," says Brown, who is also associate director of MIT's Institute for Medical Engineering and Science and a professor in MIT's Department of Brain and Cognitive Sciences and at Harvard Medical School. "Our framework lays the groundwork for two things: a clearer head post-operatively and better, more complete postoperative pain control."

■ In **Anesthesia & Analgesia:** *Multimodal General Anesthesia: Theory and Practice,* Nov. 2018, http://bit.ly/multimod-brown

Protein Linked to ID Has Unique Role in Synaptic Currents



A protein called SAP102 plays a unique role in shaping the decay of currents in postsynaptic cells.

A new study by researchers at MIT's Picower Institute for Learning and Memory has dug deeply into the molecular mechanisms that enable synaptic transmission to show the distinct role of a protein that, when mutated, has been linked to causing intellectual disability (ID).

The key protein, called SAP102, is one of four members of a family of proteins, called PSD-MAGUKs, that regulate the transport and placement of key receptors called AMPARs on the receiving end of a synapse. But how each member of the family works — for instance, as the brain progresses through development to maturity — is not well understood. The new study, published in the *Journal of Neurophysiology*, shows that SAP102 and other family members like PSD-95, work in different ways, a feature whose evolution may have contributed to the greater cognitive capacity of mammals and other vertebrates.

Specifically, the scientists found that the proteins distinctly affected how quickly electrical currents lost strength in postsynaptic cells, or neurons.

"This study is part of a continuous effort in our lab to elucidate the molecular machinery for tuning synaptic transmission critical for cognition," said senior author Weifeng Xu, an assistant professor.

In one key set of experiments, the researchers showed that while knocking out PSD-95 causes a reduction in AMPAR current frequency and amplitude, they could restore those by replacing PSD-95 with a different form, PSD-95alpha, or with SAP102.

But the two proteins are not merely interchangeable. Compared to control neurons with normal PSD-95 or cells in which PSD-95 was replaced with PSD-95alpha, cells in which PSD-95 was replaced with SAP102 had different AMPAR current kinetics, meaning that the currents took longer to decay. That timing difference made by SAP102 could make an important difference in how synapses operate to affect cognition.

In another set of experiments, the team showed that SAP102 uniquely depends on another protein called CNIH-2.

■ In **J. Neurophysiology:** *SAP102 regulates synaptic AMPAR function through a CNIH-2-dependent mechanism,* Sept. 21, 2018. http://bit.ly/Xu-SAP102

Working Memory 2.0

Important because it is mundane, working memory gets us through each day by allowing us, for example, to follow the receptionist's directions to find the doctor's office, or to sort through the costs and benefits of one set of tires versus another at the dealership. It's also profoundly debilitating when it is diminished by disorders such as schizophrenia or autism.

But MIT neuroscientist Earl Miller also sees grandeur in working memory as a system that enables our minds to exert our will over sensory information.

"What's special about working memory is that it is volitional," he said. "It is the main mechanism by which your brain wrests control from the environment and puts it under its own control. Any simple creature can just react to the environment. But what higher order animals have evolved is the ability to take control over their own thoughts."

Motivated by a desire to explain how the system works and to help people in whom it is not functioning properly, Miller has been studying working memory for more than 20 years.

In in the 30th anniversary edition of *Neuron*, Miller and co-authors Mikael Lundqvist and Andre Bastos presented a new model of working memory that explains how the brain holds information in mind (the memory part) and also executes volitional control over it (the working part).

Essentially, they posit that the brain operates working memory by coordinating ensembles of cells, or neurons, in the cortex with timely bursts of activity at the frequencies of specific brain waves. In the model, waves of alpha and beta frequencies carry our knowledge and goals in the situation (e.g. "I need tires that will last a long time but don't want to pay more than $400.") and regulate the higher frequency gamma waves that handle the new sensory information to be stored and manipulated, (e.g. the salesperson's pitch that Tire set A will last 45,000 miles and cost $360, and tire set B will last 60,000 miles and cost $420).

Meanwhile, the temporary storage of that sensory information is achieved by how the interplay of these rhythmic waves changes the weight of connections among the neurons. The new paper summarizes several lines of experimental evidence supporting the model including from papers Miller's lab published earlier this year in the *Proceedings of the National Academy of Sciences* and *Nature Communications* and in 2016 in *Neuron*.

The evidence, and the model itself, challenges at least two classically held beliefs among neuroscientists. One is that brainwaves are merely byproducts of neural activity and don't have functional meaning. The other is that working memory is maintained by a persistent hum of neural firing, rather than short, coordinated bursts. But newer and more sophisticated techniques of analysis and measurement of neural activity amid working memory experiments in lab animals have shown otherwise, the three researchers write.

■ In **Neuron:** *Working Memory 2.0,* October 24, 2018, http://bit.ly/workmem2

Remembering the directions someone just gave you requires working memory.

PICOWER PEOPLE

Fellowship Helps Postdoc Investigate Alzheimer's Mystery

Growing up, Joel Blanchard watched his grandfather remain cognitively sharp past the age of 90 but his grandmother develop Alzheimer's in her 70s. The difference sparked an interest in brain aging that motivates him today. As the new recipient of a 2018 Glenn Foundation for Medical Research Postdoctoral Fellowship in Aging Research, he will embark on research that could help explain why myelin, the insulation that clads the brain's neural wiring, breaks down in Alzheimer's disease.

"As a teenager, I wondered why these two people with shared experiences and lives had such different outcomes," said Blanchard, whose interest in Alzheimer's disease (AD) helped bring him to the lab of Picower Professor and Institute Director Li-Huei Tsai, co-founder of MIT's Aging Brain Initiative.

Myelin degeneration is one of the main mysteries of AD and brain aging more generally, Blanchard said.

With the award of $60,000 provided by the American Federation for Aging Research (AFAR) and the Glenn Foundation for Medical Research, Blanchard plans to address the question by using three-dimensional cultures of brain tissue grown from human induced pluripotent stem cells.

"We have developed a 3D model of human myelination in a tissue culture dish," Blanchard said. "This is allowing us to investigate how genetic and environmental factors associated with cognitive aging and Alzheimer's disease influence myelinating cells and neuronal health."

Using the cultures, he'll observe how they grow and change, and will be able to edit their genes to see the difference that might be made by variations associated with AD.

Blanchard said he is striving to improve understanding and to identify new approaches to diagnosing and treating the disease.

"By investigating how and why myelin degenerates in Alzheimer's disease we hope to identify new strategies for therapeutic intervention and biomarkers for identifying people at risk for cognitive impairments later in life," he said.

Earl Miller wins George A. Miller Prize

When MIT neuroscientist Earl Miller was in graduate school at Princeton, he was inspired by the lectures of George A. Miller, an influential psychologist who helped to spark the young student's interest in working memory. Now, as the newly named 2019 recipient of the George A. Miller Prize in Cognitive Neuroscience, Earl Miller is set to deliver a lecture honoring his teacher at the annual meeting of the Cognitive Neuroscience Society in San Francisco in March.

"I am honored and grateful to receive the George A. Miller Prize. I am also humbled and a little verklempt," said Miller, Picower Professor. "George was a major architect of our understanding of working memory, my major research interest."

For decades since earning his PhD at Princeton in 1990, Miller has studied working memory, "the sketchpad of consciousness" in which people can hold and control new information, such as the list of specials at a restaurant or the number of cards each of the other poker players just discarded. His lab has recently developed an entirely new model of how the system works, which he calls "Working Memory 2.0." (see p. 4). It will be the subject of his lecture at the meeting.

The model posits that working memory functions according to the interplay between two distinct rhythms that synchronize neurons in the cortex. Slower beta waves exert executive control over faster gamma waves that manipulate incoming information. Meanwhile, coordinated bursts of these rhythms control the weight of connections among the neurons to maintain storage of the information.

In awarding Miller the prize, the Cognitive Neuroscience Society is recognizing the new model's potential to shape the field.

"Each year the Prize shall recognize an individual whose distinguished research is at the cutting-edge of their discipline with realized or future potential, to revolutionize cognitive neuroscience," according to the society's website. "Extraordinary innovation and high impact on international scientific thinking should be a hallmark of the recipient's work."

Photo by: Adrianne Mathiowetz

The society has awarded the prize annually since 1995.

Left to right: Mark Bear tosses a Frisbee toward a can across Kresge Oval; In Kan Jam players try to swat the Frisbee into the can.

Putting the Fun in Funding

Sometimes fighting disease means playing games like cornhole and Kan Jam. On Sept. 20 on MIT's Kresge Oval, Picower Professor Mark Bear and members of his lab joined teams from more than 40 local biotech companies and other organizations to raise money for Fragile X syndrome research, including in his lab. Organized by the FRAXA Research Foundation, the Biotech Games raised $30,000 to advance studies of the genetic autism spectrum disorder, which is characterized by intellectual disability and behavioral and learning challenges. Bear has been studying the disease for more than a decade and has made many key insights. "We have a very real chance at a success in this disease, and it's going to have a much broader impact," Bear told a Boston Globe reporter who covered the event. "The impact in autism will be immediate, but even in the general area of psychiatric drug development," there will be an effect, he said.

> We have a very real chance at a success in this disease, and it's going to have a much broader impact.
>
> *Mark Bear*

Ludwig Family Foundation's Support Launches Study of How Alzheimer's Proteins Spread

Eugene and Dr. Carol Ludwig

Years before a person begins to show the tragic symptoms of Alzheimer's disease, such as memory loss, there has already been a buildup of toxic amyloid proteins in the brain. Scientists still don't know how the onslaught progresses, but recent observations by researchers in MIT's Aging Brain Initiative (ABI) suggest the protein affliction might spread along a bundle of nerve fibers that runs long and deep. To continue their investigation, the scientists are fortunate to have the support of The Ludwig Family Foundation, where foundation President Dr. Carol Ludwig has an interest in brain pathology that runs long and deep, too.

A second-generation neurologist, Dr. Ludwig knows how urgently advances in Alzheimer's disease research are needed and yet how much scientists and physicians still need to understand about neurodegeneration. When she learned that Professors Li-Huei Tsai and Ed Boyden were pursuing a project that might show how amyloid propagates early in the disease, she decided it was important to help.

"We felt it had the potential to further advance knowledge in the area and to hopefully provide valuable data that would lead to further investigation and future support," she said. "While the project had its risks, the questions were worth exploring."

Indeed, for scientists to pursue a new lead at an early stage, it's vital to have the support of knowledgeable philanthropists, who are willing to back projects before they are far enough along to gain traditional research funding, said Tsai, a co-founder of the ABI and director of the Picower Institute for Learning and Memory.

"When we first saw that amyloid might be disrupting and spreading along these crucial long-ranging circuits early in the disease, we knew we had to investigate what was going on," Tsai said. "We are very grateful for The Ludwig Family Foundation's support because it is allowing us to do experiments that will help us develop a greater understanding."

> We feel strongly that the research of today will provide the treatments of tomorrow.
>
> ***Dr. Carol Ludwig***

Findings in the fornix

The research began when Tsai and Assistant Professor Kwanghun Chung mapped amyloid across the whole brains of Alzheimer's model mice. At that scale, they saw that in early stages of the disease, amyloid buildup was especially prevalent along a long-ranging conduit of nerve fibers called the fornix. The structure forms an arc that curls around the inside of the brain, providing crucial connections between subcortical structures and the hippocampus, a region vital for long-term memory. In particular, the proteins afflicted the "white-matter" sheath around the conduit.

Could amyloid be spreading around the brain via this neural highway? Tsai and Boyden, also an ABI co-founder, resolved to find out and, with The Ludwig Family Foundation's support, have embarked on two sets of cutting-edge experiments. In one they plan to get a close-up view of amyloid deposits in the fornix using a technique Boyden developed to physically enlarge tissue details too small to be resolved by microscopes. They hope to pinpoint exactly how amyloid resides in the fornix.

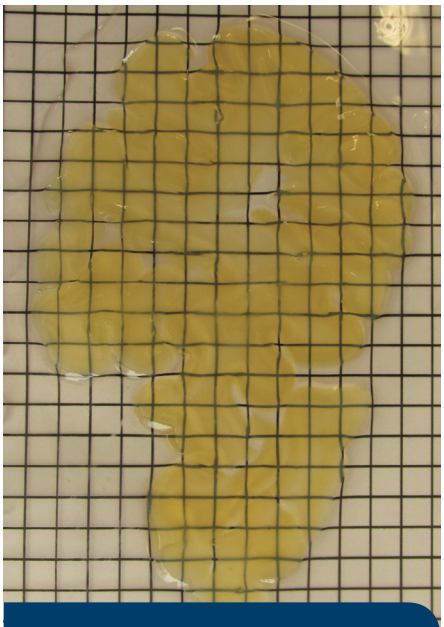
In the second set they will use another technology Boyden co-developed to determine whether and how brain activity might drive amyloid propagation. "Optogenetics" allows them to stimulate neural activity using light, so they can induce activity in precise locations and then measure its effects.

Dr. Ludwig said it's important that a system-wide investigation of Alzheimer's disease is led by a partnership between researchers across disciplines. Boyden is a neuroengineer and Tsai is an expert in neurodegeneration.

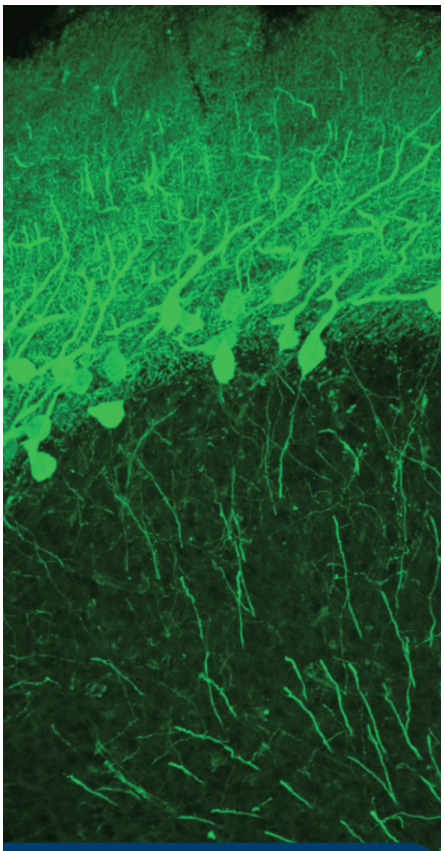
"Focusing on the brain in Alzheimer's as a system dysfunction appears like a logical next step and we felt strongly that the open, collaborative and interdisciplinary nature of MIT and the Aging Brain Initiative was the best way to advance knowledge in the field," she said.

"We are fortunate and privileged to be able to be part of the philanthropic community and to be able to aid, albeit in very small ways, the advancement of scientific knowledge," she said. "Without support for research, the ultimate goal of helping people will remain elusive.

"We feel strongly that the research of today will provide the treatments of tomorrow."



A 2mm thick slice of human brain treated with processes to make it durable and clear.



Purkinje neurons in the cerebellum resolved using SHIELD and MAP.

Chung leads new collaboration to make the best brain map yet

Nowadays anyone with a map app can explore the whole world in whatever level of detail they want. With a new grant from the National Institutes of Health, a team led by Kwanghun Chung intends to usher in a similar revolution for neuroscientists, giving them an unprecedentedly detailed and complete map of the human brain.

"It will be the first subcellular resolution, true volumetric human brain map," said Chung, assistant professor in the Picower Institute, the Institute for Medical Engineering and Science and the Department of Chemical Engineering. "It will be like Google Maps. You will be able to drill all the way down to see what's inside of individual 'buildings' and all the way up to see the 'Earth'."

Except in this simile the "buildings" are cells and the "Earth" is a whole human brain with all of its complex integration of circuits and regions. Truly a map – not just a detailed picture – the technology Chung's team plans to implement will resolve specific proteins in individual cells, allowing scientists to identify their type and function. This is the equivalent of Google Maps not just showing you a picture of two MIT buildings across from each other on Vassar Street, but also revealing that in Building 46 there are neuroscientists and in the Stata Center there are roboticists.

Producing a human brain map of this unprecedented scale, detail and multidimensionality could reveal entirely new types of brain cells and previously unknown connections, Chung said. Moreover, after the team implements all the technologies and methods needed to accomplish the first map, costs will invariably begin to come down, potentially leading to a revolution in brain mapping akin to genome sequencing.

"This will be the first demonstration, but after we have achieved this, we will be able to map many more brains with all sorts of neurological disorders and with decades-long medical records and functional data," Chung said. "There are hundreds of brain banks worldwide and many tens of thousands of brains available. If we can map many brains, we will be able to learn a lot."

CEREBRAL CARTOGRAPHY

The team's plan for mapping two whole brains will begin at Massachusetts General Hospital (MGH) where collaborator Dr. Matt Frosch, a world-renowned pathologist, the director of the MGH brain bank, and the associate director of HST, will carefully examine brains at autopsy to select two samples that are as "normal" as possible. Dr. Van Wedeen, an associate professor of Radiology at Harvard University and MGH, will then scan the intact brains with MRI to resolve their overall structure and connectivity.

From there the brains will travel to MIT where Chung's lab will slice them into 2 millimeter-thick slabs (yielding about 60 per brain) and then apply a series of innovative tissue processing methods that Chung has devised. SHIELD allows for a brain to be optically cleared while protecting the structure of every cell and protein and preserving their ability to react with a wide variety of fluorescent labeling agents applied using another chemical process called SWITCH. With the slabs preserved and labeled, the team will be able to scan them using custom-built microscopes with subcellular resolution but also high throughput. After the slabs are scanned, the team will zoom even further in on key areas of interest using MAP, another Chung invention that allows for tissues to be enlarged so that their tiniest structures become resolvable to microscopes.

All these incredibly detailed yet full-scale images will produce an enormous amount of data – Chung estimates about 40 petabytes, (40 million gigabytes). That's why team members Sebastian Seung at Princeton, Laura Brattain at MIT's Lincoln Laboratory, and a group of computer scientists in the Chung lab are working together to develop special image processing algorithms.

In all, the project will incorporate many of Chung's best tissue processing inventions and lead to the invention of even more new technologies. That's what it takes to map the human brain, which is 2,000 times the volume of a mouse brain.

"It's something that we have been preparing since I joined MIT," Chung said. "Now I feel like we are ready to attack this challenge." The development of the technologies was supported by the JPB Foundation, NCSOFT Cultural Foundation, the Burroughs Wellcome Fund Career Award at the Scientific Interface, the Searle Scholars Program, the Packard Award in Science and Engineering, the McKnight Foundation Technology Award, and the National Institutes of Health.

Above: Picower Professor Li-Huei Tsai stands the in main lobby of the San Diego Convention Center. Below: Tonegawa Lab graduate student Chen Sun enthusiastically explained his poster to crowds of visitors for hours.

At 'SfN' Picower Researchers Engage in Neuroscience's Largest Annual Exchange of Ideas

Scores of Picower Institute researchers traded a view of leaves falling along the north bank of the Charles River for that of palm trees along the shore of the San Diego Bay Nov. 3-7. The Society for Neuroscience Annual Meeting is all about expanding one's perspectives, both by seeing the latest work of other neuroscientists and showing one's own to them.

The mammoth conference, which this year drew nearly 30,000 people from all over the globe, annually presents a huge opportunity for neuroscientists to network, hear about broad trends in the field, keep tabs on what other labs are up to, and to browse the latest lab equipment. But for one moment, be it at a poster or at a lectern, those who are presenting have a forum to influence the field and to sample the field's feedback by sharing their latest work.

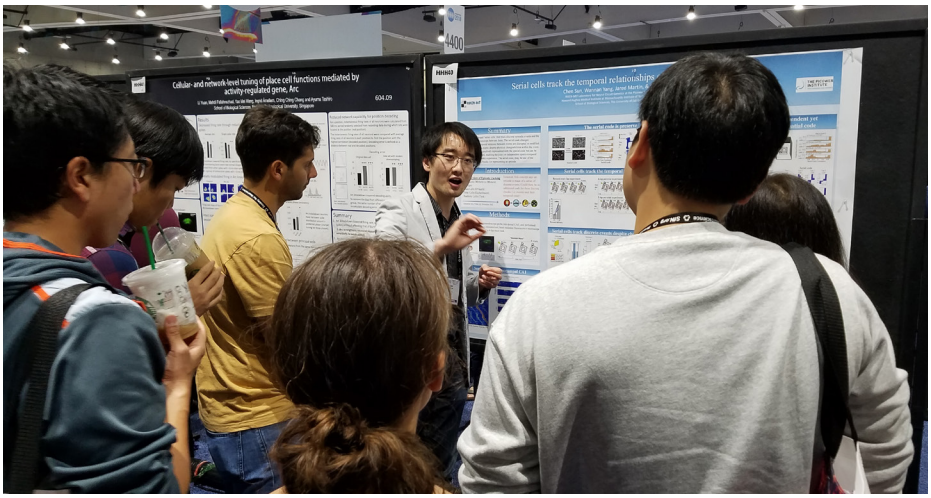
In all, Picower faculty members, postdocs and students presented more than 40 talks and posters on topics ranging from brain circuits underlying compulsive drinking, to hippocampus cells that track the order in which experiences happen, to the brain mechanisms underlying anesthesia, to advances in microscopy. Kwanghun Chung co-chaired and spoke at a symposium on whole-brain tissue imaging and analysis, Kay Tye moderated a press conference on the neuroscience of social behavior, and faculty members such as Earl Miller, Li-Huei Tsai and Tye spoke at some of the myriad satellite events that surround the conference. Miller presented his new model of working memory (see p. 4), Tye discussed how the brain assigns positive or negative feelings to experiences, and Tsai discussed her lab's research on the APOE4 gene variant that conveys an elevated risk of Alzheimer's disease.

In the aggregate, Picower presenters demonstrated many ways in which the Institute's research contributes to the broader field. In turn, the questions and comments they received from colleagues at the conference provided them valuable ideas as well.

This was the third SfN for Nicole Aponte Santiago, a graduate student in the lab of Professor Troy Littleton. This year she presented twice. On Nov. 4 she spoke on a panel offering advice about professional networking and the next day displayed a poster on experiments probing how the competitive interplay that arises when multiple neurons connect to the same muscle affects the development and growth of those connections.

Two years ago, when she last attended the conference, her project was just getting started. She said that visitors to her poster shared helpful thoughts and suggestions about the research and a lot of encouragement that it would be important.

"People were showing a lot of interest in my project which made me even more excited and made me feel that OK, this is something useful for people in my field," she recalled. "People were excited to see what results I would get."



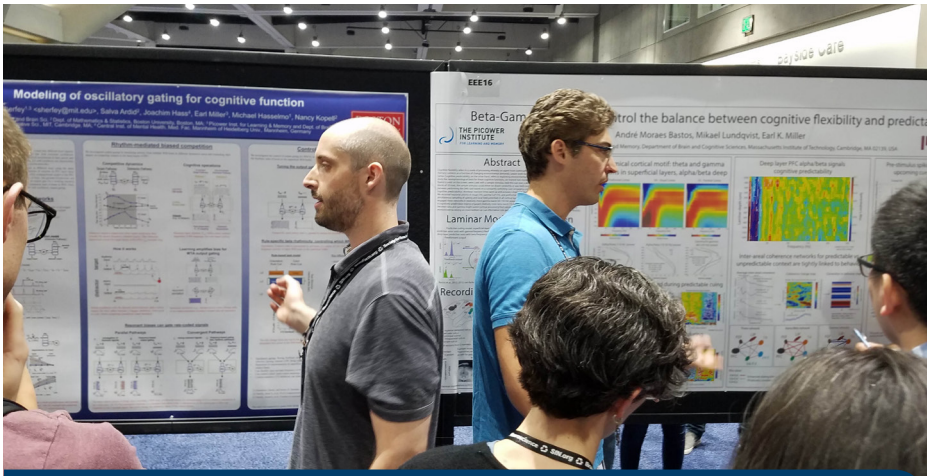
This year some of those same people returned to her poster, she said, and they were excited to see how the experiments have been taking shape. Visitors asked good questions and offered interesting interpretations of her results as well as ideas for new experiments and methods, she said, providing her a new dose of encouragement.

Visitor traffic kept some poster presenters on their feet and surrounded for hours, ringed by a crowds four or five people deep. Chen Sun, a graduate student in Susumu Tonegawa's lab spent the entire afternoon of Nov. 6 energetically explaining his research showing that "serial" cells in the hippocampus uniquely keep track of sequences of events – such as laps in a race. For the whole afternoon his audience was never less than about a dozen people.

Josiah Boivin, a postdoc in the lab of Professor Elly Nedivi, fielded a slew of questions as he discussed the lab's innovative two-photon microscope that radically speeds up imaging by scanning a whole line at a time rather than point by point. He plans to use the technology to more closely monitor and study the frequent assembly and removal of inhibitory neural connections, or synapses, in live animals, which could help explain how neural connections change with experience.

Tsai lab graduate student Mitchell Murdock, meanwhile, entertained strong traffic at a poster describing how he uses a technique called Archon, developed in Professor Ed Boyden's lab, that engineers neurons to visually report their electrical activity by glowing, which can make measuring electrical activity easier. Murdock, who studies Alzheimer's disease, is using the technology to determine the role of individual cells in the apparent breakdown of key brain rhythms in the condition.

Posters and talks are grouped by topic at SfN so Picower presenters were often together. Chloe Delepine and Jennifer Shih, postdocs in the lab of Mriganka Sur, stood side by side the morning of Nov. 6 amid a gaggle of visitors as they explained how the activity of non-neural brain



Jason Shefrey and Andre Bastos stand back to back explaining their posters on the significance of brain rhythms in cognition.

cells called astrocytes appear to be indicative of and influential in the activity of neurons in the motor cortex as mice learn new movement tasks. Andre Bastos, a postdoc in the Miller lab and Jason Shefrey, a Miller lab collaborator at Boston University, were cornered back-to-back among a throng of inquirers into their research on how brain rhythms govern the flow of information in the cortex and other brain regions. And directly on the other side of the poster wall from Boivin's poster on rapid imaging of synapses was that of Littleton lab graduate student Elizabeth Brija, who studies how RNA editing regulates a protein called complexin, which is an important component in how synapses change in response to activity.

At different times the Chung and Tye labs each commanded neighborhoods four or five posters long. Tye lab members Cody Siciliano, a postdoc, and Habiba Noamany, an undergraduate at her first SfN, reported on different aspects of how a particular circuit between the prefrontal cortex and a deep region called the periaqueductal gray appears key to encoding aversive experiences. When the circuit is inhibited, they found, animals are more likely to disregard aversive stimuli including ones that would otherwise curb their consumption of alcohol. The Chung lab, meanwhile, showed off several new techniques dedicated to exposing, preserving and labeling the brain's full anatomy, connectivity, and functionality for imaging at scales from molecules and synapses to the whole organ. At his talk on Nov. 6, Chung described how he's brought this suite of tools to collaborations with Tsai, to locate harmful proteins early in Alzheimer's disease and with Tonegawa to trace memory engrams all around the brain. He also mentioned his new grant to map the entire human brain (see p. 7).

With a crowd big enough that people were standing in the back, Miller lab graduate student Jacob Donoghue described how general anesthesia causes information flow among brain regions to become incoherent and fragmented but that consciousness can rapidly be restored by stimulating the thalamus. Speaking the next day, two members of Professor Matt Wilson's lab, postdoc Honi Sanders and research scientist Hector Penagos, discussed their studies using rodent experiments and theoretical models to understand how representations among hippocampal neurons allow the brain to learn and remember the distinguishing features of environments and how to best navigate environments to maximize rewards.

Was SfN itself a rewarding experience? Aponte said she drew inspiration from her encounters at the conference. And so did Sun, even after explaining his poster on serial cells at marathon length yet at the pace of a full sprint. Like a distance runner, he described feeling both elated and exhausted when it was all over.

"They were very enthusiastic," Sun said of his audience. "Because they were very enthusiastic, it kind of feeds back. That's why four hours felt like half an hour."

Picower speakers Jacob Donoghue, Honi Sanders and Hector Penagos.

Innovations Giving Neuroscientists Exciting New Ways to Gain Insights, Symposium Speakers Say

Hundreds of people who attended the Picower Institute for Learning and Memory's Fall Symposium "Frontiers in Neurotechnology" Oct. 23 got an inside look at many ingenious new ways to look inside the brain, both to understand its healthy anatomy and function and to better understand disease.

The emerging techniques and methods presented by 10 leading researchers – improvements in microscopy, advances in culturing brain tissues, and novel ways to detect and control brain activity – illustrated the fast pace of innovation in neuroscience today, said Li-Huei Tsai, Picower Professor and director of the Picower Institute.

"We are very fortunate to be working in neuroscience at a time of such extraordinary ingenuity," she said.

IMPROVING INSIGHT

Some of the new techniques that Tsai and hundreds of colleagues worldwide are adopting, including methods of preserving, optically clearing, labeling and enlarging brain tissue for spectacularly informative imaging, were invented by the symposium's host, MIT Assistant Professor Kwanghun Chung. He revealed that he is leading a new five-year project funded by the National Institutes of Health to map the entire human brain at unprecedented scales of detail (see page 7). He's also been applying the techniques to trace the circuits connecting brain regions key to the Parkinson's disease treatment deep-brain stimulation, and to illuminate differences between models of the autism-like condition Rett Syndrome and healthy controls.

Advanced tissue processing, though, is just one way neuroscientists are getting a better look at the brain. Several speakers discussed major leaps in microscopy. Elizabeth Hillman of Columbia University, for example, discussed her ongoing development of "SCAPE," a version of light-sheet two-photon microscopy in which scopes image a broad plane of tissue rather than just a narrow spot. She showed how SCAPE is fast and sharp enough to allow real-time imaging of neural activity and blood flow in entire brains of behaving animals such as zebrafish and fruit flies, entire bodies of nematode worms, and large brain volumes in mice.

Na Ji of UC Berkeley described a different way of imaging activity within large brain volumes in live animals. She's used the "Bessel beam" system to simultaneously image all the dendrites and synapses of a neuron (in 3D) in the visual cortex to watch how it responds to specific sensory inputs. What would take 10 hours with a conventional scope took 20 minutes using the technique, she said.

Ji and fellow speaker David Kleinfeld both pointed to another technology: adaptive optics, which dynamically adjusts the mirrors of a scope to mitigate distortions from light bending within complex tissues. By working to optimize parameters of two-photon microscopy, including the use of adaptive optics, Kleinfeld's lab has been able to image cortical layers 800 microns (0.8 mm) deep.

> We are very fortunate to be working in neuroscience at a time of such extraordinary ingenuity.
>
> *Li-Huei Tsai*

Another way speakers showed progress in seeing into the brain was in developing new kinds of "reporters," or molecules that fluoresce when they encounter a target chemical or protein. Kleinfeld, for example, has developed reporters

Kwanghun Chung discusses the many tissue processing methods his lab has developed.

Photo by: Lindsey Michelle Williams

Emery Brown discusses his research on technology to improve anesthesiology.

called CNiFERs that show the concentration of neurotransmitters. Boaz Levi of the Allen Institute discussed his work to develop reporters for an entirely different purpose: distinctly marking different cell classes and types in human and mouse cortex using engineered viruses. His goal is to help neuroscientists better sort through that complex landscape.

Yet another way to get a readout of brain activity is to monitor its large-scale oscillations, or brain waves. Though known for decades, brainwaves still have huge untapped potential to inform researchers and clinicians alike, said Emery N. Brown the Edward Hood Taplin Professor at MIT. By advancing rigorous statistical methods to analyze EEG readings of patients under general anesthesia, Brown has been able to create systems that allow for monitoring a patient's brain state in real time. The work has shed light on how anesthesia works, how people respond at different ages, and has led to innovations in medical practice that allow anesthesiologists to better control drug doses, often allowing for dramatic reductions in the amount of medicine administered, Brown said (see p. 3). That, in turn, can help patients wake up faster and clearer-headed yet with better-managed pain. The next step in Brown's work, he said, is developing a real-time, closed loop system that can regulate dosing in response to EEG readings.

MAKING 'MINI-BRAINS'

For ethical and logistical reasons, scientists often need to experiment with lab-grown neural tissue cultures rather than actual brains. Several speakers at the symposium shared their latest innovations in the burgeoning field of culturing 3D brain organoids, or mini-brains, which can provide otherwise unattainable insights. Organoids are considered valuable because they can be grown from reprogrammed cells taken from human patients, or other organisms, and then developed into models that reflect brain development with those same genes. Moreover the genes can be precisely manipulated in the lab.

Sergiu Pasca of Stanford University offered several examples. For instance, in a new study his lab is examining the effects of oxygen deprivation on cells in the developing brain, a problem that sometimes affects fetuses.

In her talk, Paola Arlotta of Harvard University emphasized the need to ensure that organoids provide reproducible experimental testbeds. After all, it's one thing to grow tissues but it's another to make reliable experimental comparisons using them. She discussed work her lab has done to improve organoid culture to ensure greater reproducibility.

Orly Reiner of the Weizmann Institute in Israel said her lab is interested in understanding lissencephaly, a disease characterized by a lack of characteristic folds on the surface of the brain. But as organoids grow, if they don't have vasculature, cells embedded deep inside can't get nutrients they need and die. Moreover without some of the kinds of innovations described above, microscopes cannot image those inner cells clearly. So Reiner's lab decided to grow organoids on a chip, reshaping them into more of a thin disk shape that could be imaged and sustained. The models have indeed provided important insights into the disorder.

Arnold Kriegstein of UC San Francisco has also used organoids to study lissencephaly and other disorders. His lab has a more general interest in a particular class of progenitor cells that give rise to neurons during development. He found that these progenitor cells behave abnormally in the lissencephaly model. Meanwhile, members of his lab also use organoids to make comparative evolutionary biology studies of brain development among humans, chimpanzees and macaque monkeys.

At the end of the day, Matthew Wilson, Sherman Fairchild Professor in Neurobiology at MIT and associate director of the Picower Institute summed up the optimism of the field.

"This is the frontier," Wilson said. "Thinking about these technologies that are giving us access to describe and understand the complexity of the brain at the level of molecules, cells and systems and then using that to turn around and understand how we can control brain function and understand cognition, it really is a golden age."

Upcoming Events

For the *latest* information on all our lectures, symposia and other events, please visit: **picower.mit.edu/events**

SAVE THE DATE *of* **OCTOBER 16**

For the Picower Institute Fall 2019 Symposium "Neural Mechanisms of Memory and Cognition"

01.25.19 Special Seminar
Kazuo Tsubota, MD, Keio University School of Medicine

02.19.19 Aging Brain Initiative Seminar
Michael Heneka, PhD, University of Bonn

04.04.19 MIT Colloquium on Brain & Cognition
Zachary Mainen, PhD, Champalimaud Research

04.23.19 Picower Lecture
Karel Svoboda, PhD, HHMI's Janelia Research Campus

All lectures, seminars and colloquia start at 4 p.m. in Singleton Auditorium, Building 46

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

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BOTTOM ROW: Elly Nedivi, Professor, Departments of Brain and Cognitive Sciences and Biology; **Mriganka Sur**, Paul E. Newton Professor of Neuroscience, Director of The Simons Center for the Social Brain; **Susumu Tonegawa**, Picower Professor of Biology and Neuroscience, Departments of Brain and Cognitive Sciences and Biology, Investigator, Howard Hughes Medical Institute, Investigator and Director of the RIKEN-MIT Center for Neural Circuit Genetics; **Li-Huei Tsai**, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Director, The Picower Institute for Learning and Memory; **Kay Tye**, Associate Professor of Neuroscience, Department of Brain and Cognitive Sciences; **Matthew Wilson**, Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology, Associate Director, The Picower Institute for Learning and Memory; **Weifeng Xu**, Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences.