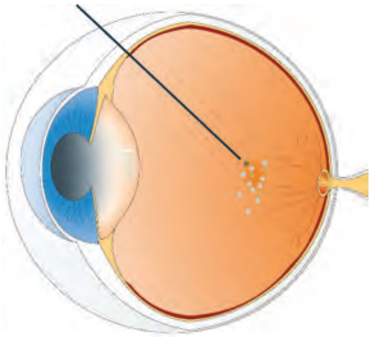
2019

Berkeley Neuroscience
HELEN WILLS NEUROSCIENCE INSTITUTE

Pulse

Gene therapy restores vision in blind mice, holds promise for humans



The gene for a light-sensitive protein was delivered to retinal ganglion cells at the back of the eye by injection of a modified virus into the center of the eye, endowing these cells with the ability to detect light.
Image by John Flannery.

The Berkeley Neuroscience labs of **Ehud Isacoff** and **John Flannery** have restored vision in blind mice using a modified virus to deliver a gene for a light-sensitive receptor to the retina. The breakthrough holds promise for patients with visual impairment due to inherited or age-related retinal degeneration. "You would inject this virus into a person's eye and, a couple months later, they'd be seeing something," Isacoff envisions.

Retinal degeneration typically affects photoreceptor cells that detect light but spares downstream cells, such as retinal ganglion cells (RGCs). Using a virus that infects RGCs, the team delivered the gene for medium wavelength opsin, which detects yellow-green light in cone photoreceptors. This enabled the RGCs to respond to light. When injected into the eyes of mice blind due to retinitis pigmentosa — a leading cause of inherited blindness in humans — the procedure restored their vision to a level comparable to mice with normal vision.

While similar approaches have been attempted with genes for other proteins, this is the first with the sensitivity, speed, and ability to adapt to changes in light levels necessary to restore functional vision, such as the ability to detect objects and moving patterns in typical indoor and outdoor lighting.

The findings were reported in *Nature Communications* (March 2019) by a team that includes Berkeley Neuroscience PhD student **Krisha Aghi**, alum **Benjamin Gaub**, and postdoctoral fellow **Julia Veit**. Isacoff and Flannery are currently raising funds to begin gene therapy trials in humans in the next three years.

Daniela Kaufer and William Jagust win the 'Radical Ideas in Brain Science Challenge'

There are currently no effective treatments for Alzheimer's disease (AD) and age-related cognitive decline, conditions that impact the lives of many people. Berkeley Neuroscience members **Daniela Kaufer**, Professor of Integrative Biology, and **William Jagust**, Professor of Public Health, hope to change this by investigating the degradation of the blood-brain barrier (BBB) as a possible new cause of dementia.

Their project was the winner of the 2018 *Radical Ideas in Brain Science Challenge*, managed by Berkeley Neuroscience and made possible by the generosity of Berkeley Brain Initiative donors. This was the second year of the *Challenge*, which provides critical funding to catalyze groundbreaking discoveries in neuroscience. The focus of the *Challenge* this year was "The Aging Brain". Kaufer and Jagust will receive an award of up to $190,000 over two years to test their hypothesis that age-related degeneration of the BBB is a cause of AD and other dementias.

The BBB protects the brain from harmful substances in the blood. When it degrades with age, proteins can leak in, causing inflammation and cognitive impairment. Kaufer, an expert on aging and the BBB in rodents, and Jagust, an expert on aging and dementia in humans, will be the first to directly compare BBB dysfunction in older people to the presence of molecular markers of AD and memory function. They will also use rodents to explore the molecular mechanisms that may be involved. Ultimately, their findings could lead to new avenues for the diagnosis and treatment of these widespread and devastating conditions.

A Message from our Directors

Ehud Isacoff

Director, Helen Wills Neuroscience Institute and Berkeley Brain Initiative (2013-present)
Professor of Neurobiology, Molecular and Cell Biology Department

The people of Berkeley Neuroscience make it what it is — a vibrant, innovative, interdisciplinary community that sheds light on the mysteries of the nervous system through research in individual labs and unique collaborations. Adding new faculty opens up new opportunities, and I'm thrilled to welcome our newest members: **Lexin Li** (Public Health, Biostatistics and Epidemiology), **John Clarke** (Physics), **Michel Maharbiz** (EECS), **Ellen Lumpkin** (MCB), and **Emily Cooper** (Optometry & Vision Science). I also want to congratulate our faculty, postdocs, and graduate students who were honored with prestigious awards this year!

In 2018, UC Berkeley's Vice Chancellor for Research, Randy Katz, wrote about the connection between use-inspired research — fundamental research with relevance to real-world issues — and the Nobel prize winners associated with Berkeley. This approach also drives research within Berkeley Neuroscience. This year, members published many articles related to brain health, from neurodevelopmental disorders to neurodegenerative diseases, as well as socially relevant issues such as bias and discrimination.

Brain aging is an important area of research that has widespread impact on individuals and society. This year, we were pleased to offer the *Radical Ideas in Brain Science Challenge* on the topic of "The Aging Brain," thanks to the generosity of visionary philanthropic partners.

Many of our members embrace and invent new technologies to help us understand the brain in health and disease. You can read about some of our innovations and discoveries in this issue. We are excited about new collaborations between Berkeley and institutions like UCSF that can help turn scientific discoveries into treatments, or even cures, for patients.

In the next year, we are looking forward to having a new class of PhD students join our community and continuing our creative and cutting-edge research to advance science and improve lives.

Michael Silver

Director, Neuroscience PhD Program (2017-present)
Associate Professor of Optometry and Vision Science

This year the Berkeley Neuroscience PhD Program reached a milestone — our one hundredth graduate! Our program has now been in existence for 19 years, and our alumni are making meaningful contributions to the world in a variety of careers, including faculty members at outstanding universities, researchers in industry, and CEOs.

Emily Cooper, who graduated from the PhD Program in 2012, became an Assistant Professor in the UC Berkeley School of Optometry and joined Berkeley Neuroscience this year, making her the first person to be both a graduate student and faculty member in our program.

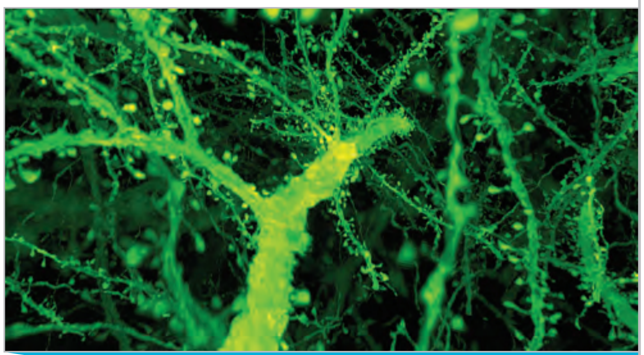
Congratulations to **Katie Arnemann**, **Keven LaBoy**, **Amy LeMessurier**, **Falk Lieder**, **Kim Long**, **Elizabeth Lorenc**, **Alex Naka**, **Anwar Núñez-Elizalde**, **Elena Ryapolova-Webb**, **Vlad Senatorov**, and **Wren Thomas**, all of whom obtained their Neuroscience PhD in 2018. These students comprised the largest graduating class in the history of our program, and we are excited to see what their future will bring. We also welcomed an impressive group of first-year graduate students: **Erin Aisenberg**, **Marisa Becerra**, **Julia Bleier**, **Katie Cording**, **Matt Davis**, **Mark Gorenstein**, **Azure Grant**, **Madeline Klinger**, **Sonali Mali**, and **Brett Nelson**. Also, congratulations to **Hayley Bounds**, **Celia Ford**, and **Kevin Yu** for being awarded National Science Foundation Graduate Research Fellowships this year.

In the coming year, I look forward to learning about the groundbreaking discoveries that will be made by our graduate students and faculty, strengthening the Berkeley Neuroscience community, and continuing to improve the quality of training, education, and development of the next generation of neuroscientists.

Publications

RESEARCH DISCOVERIES

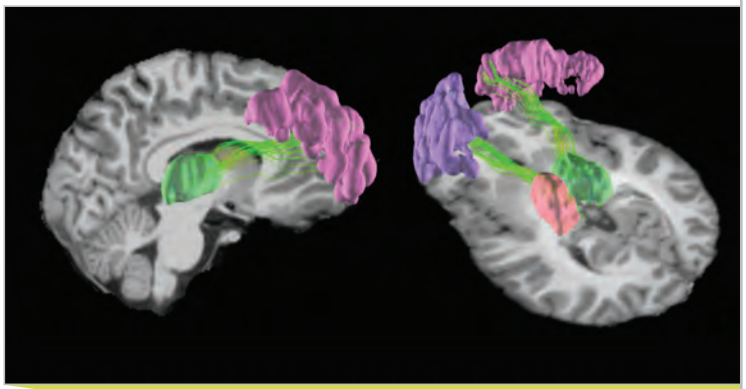
Breakthrough in microscopy allows rapid visualization of neural networks across the entire fly brain



Rounded spines protrude from dendrites on neurons in the mouse cortex.
Image courtesy of Eric Betzig.

Nobel laureate **Eric Betzig** and collaborators, including Ed Boyden at MIT, have developed a method that can produce high-resolution images of all the dopamine neurons in a fruit fly brain — at the astonishing speed of just three days. By combining lattice light-sheet microscopy, invented by Betzig, and expansion microscopy, invented by Boyden, they were able to create a 3D reconstruction of these neurons throughout the brain, including all 40 million synapses. In the study, published January 2019 in *Science*, the researchers also showed that their method can be successfully used to visualize circuits across the mouse cortex. In the future, it may even be possible to use it to map the connections of the human brain.

Playing just one season of football causes brain changes that correlate with head impacts



Highlighted regions in the front, back, and interior of the brain show where microscopic brain changes occur after a season of football.
Image by Nan-Jie Gong and Chunlei Liu.

Repeated concussions over an athlete's career are well known to cause damage to the brain, but what about less severe head impacts over a shorter period of time? To find out, **Chunlei Liu** and collaborators examined the brains of high school football players with MRI before and after a single football season. Although none of the players experienced concussions, the researchers found significant changes in the microstructure of cortical gray matter in the front and back of the brain where impacts are most likely to occur, as well as changes to deeper brain structures, after just one season. The brain changes were correlated with head impacts recorded by devices in the players' helmets. The study was the cover story of the November 2018 issue of *Neurobiology of Disease*.

Quantifying how stereotypes lead to discriminatory behavior

Stereotypes based on characteristics such as ethnicity and gender lead to unequal treatment in many areas of life, including health care, education, and employment. To better understand the relationship between stereotypes and how people treat others, **Ming Hsu** and colleagues developed a computational model that quantifies and predicts how stereotypes — based on the perceived warmth and competence of particular groups — affect how much money members of these groups are given in an economic game. Their model fits real-world data on discrimination in hiring and higher education. The research was published in September 2018 in the *Proceedings of the National Academy of Sciences*.

Publications

RESEARCH DISCOVERIES

Developing a 'pacemaker' for the brain

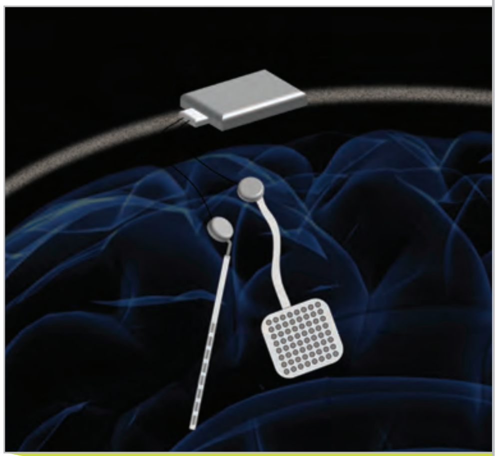


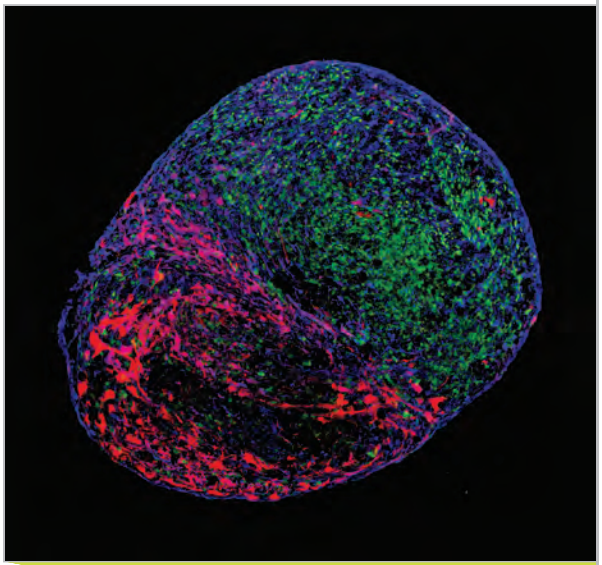
Image by Rikky Muller.

Rikky Muller, **Jose Carmena**, and colleagues have developed an implantable wireless device called WAND that can autonomously monitor electrical activity in the brain, detect aberrations, and apply a tailored amount of stimulation in response. WAND is groundbreaking because it can simultaneously monitor subtle brain activity while delivering relatively large amounts of stimulation, allowing it to more accurately regulate brain activity in real-time than previous devices. The study, published in *Nature Biomedical Engineering* in December 2018, demonstrated use of the device in non-human primates. In the future, it could be used to treat conditions that involve altered neural activity such as epilepsy or Parkinson's disease.

Study challenges dominant hypothesis of autism

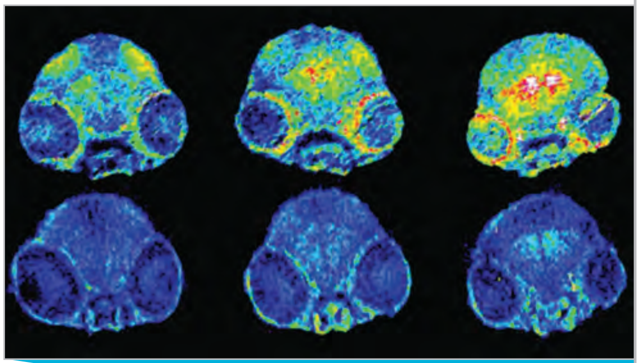
Autism symptoms have been postulated to result from excessive neural firing due to an imbalance between excitation and inhibition in the brain. A study from **Dan Feldman's lab** published in *Neuron* in February 2019 calls this prevailing "excitation-inhibition" hypothesis into question. They analyzed four mouse models of autism and found that despite alterations in the ratio of excitation to inhibition, there was no resulting increase in the rate of neural firing. Rather, changes in inhibition exactly compensated for changes in excitation, resulting in a normal rate of firing. This suggests that proposed treatments for autism that simply increase inhibition may not be successful, and that other, more nuanced approaches are needed to understand and treat this disorder.

Human brain organoids: A new way to study conditions such as autism and epilepsy



Human cortical spheroid showing normal neurons (green) and astrocytes (a type of glial cell; blue) generated from cells where only one copy of the TSC2 gene was inactivated; and enlarged, dysmorphic cells (red) from cells where both copies were inactivated, forming a "tuber-like" region. Image from the Bateup lab.

The developmental disorder tuberous sclerosis complex (TSC) causes the formation of cortical tubers — disorganized regions of abnormal cells in the cerebral cortex — and often results in epilepsy, autism spectrum disorder, intellectual disability, and psychiatric disorders. A study from **Helen Bateup's lab** published in *Nature Medicine* in August 2018 described how they used 3D cultures and CRISPR-Cas9 gene editing in human cells to generate the first model of TSC that replicates the tubers seen in patients. Their findings also shed light on how stem cells acquire either a neuronal or glial cell fate in the developing human cortex and how somatic mutations — those not passed down through the germ line — can lead to disease states.



Copper visualized in the brains of wild type (top row) and mutant (bottom row) zebrafish. Image from Tong Xiao, Chang Lab.

Copper in the brain: Mining a mineral that regulates sleep and wakefulness

Copper is highly concentrated in the brain, and one area of the brain — the locus coeruleus (LC) — has the highest levels of copper. What is all this copper doing in the LC? In a study published in *Nature Chemical Biology* in June 2018, researchers from the **Chang** and **Isacoff** labs found that mutant zebrafish deficient in brain copper were sluggish during the day and more active at night, indicating that copper regulates sleep-activity cycles. Their evidence suggests that copper regulates these cycles by promoting synthesis of norepinephrine in the LC. This could have implications for human conditions such as Alzheimer's disease, Parkinson's disease, and autism, which all involve altered copper homeostasis.

Read more about these and other research discoveries on our website: neuroscience.berkeley.edu/category/research-discovery/

Kevin Weiner

HISTORICAL RESEARCH

Burt Green Wilder debunked biased claims about brain size and pioneered neuroscience outreach to children

While researching the history of a brain area that he studies, Assistant Professor of Psychology **Kevin Weiner** stumbled upon mention of anatomist Burt Green Wilder (1841-1925) and became fascinated with this outspoken critic of shoddy science and champion of neuroscience education. In a publication in the *Journal of the History of the Neurosciences* in October 2018, Weiner described how Wilder disproved flawed theories about brain size that were being used to support racial and gender discrimination, conducted the first "Brain Day" to teach children about the brain, and advocated for standardized neuroanatomical nomenclature.

Marla Feller

PERSPECTIVES

Why scientists should embrace teaching

In a NeuroView article published in *Neuron* in September 2018, Professor of Neurobiology **Marla Feller** made the case that teaching undergraduates is not only personally satisfying, but also helps advance science in several ways, including prompting scientists to think more broadly about their own research.

Hillel Adesnik

A holistic approach to understanding sensory perception

In a Perspective published in *Neuron* in December 2018, Associate Professor of Neurobiology **Hillel Adesnik** and recent PhD Program graduate **Alexander Naka** proposed an "experimental road map" to answer open questions about the function of cortical layers in sensory processing, by combining multiple new and emerging technologies to study the cortex from individual cells to large-scale circuits.

Read more about these and other perspectives on our website: neuroscience.berkeley.edu/category/perspective/

PhD Program Alumni Profiles

Studying vision in the real world and applying it to virtual worlds

Emily Cooper returns to Berkeley as faculty

"To understand any perceptual system, such as the human visual system, you also have to have a deep understanding of the natural environments in which that system evolved to operate, and the tasks that the organism needs to perform."

Emily Cooper,
entering class of 2007

Emily Cooper is an Assistant Professor in the School of Optometry & Vision Science Program and a member of Berkeley Neuroscience, making her the first alum to join the program as a faculty member. Cooper's research focuses on human visual perception, particularly in three dimensions, and how it is used in natural environments. She also uses her findings about vision to help make better display technologies, such as those used in virtual and augmented reality, in collaboration with industry partners.

As a PhD student, Cooper studied 3D visual perception in the lab of **Martin Banks**. During her postdoc in Anthony Norcia's lab at Stanford, she began applying her research to display technologies. Before returning to Berkeley, Cooper was a faculty member at Dartmouth College. Cooper explains why she chose Berkeley Neuroscience for graduate school: "[It] was right in that sweet spot of interdisciplinary neuroscience training. Interdisciplinary training was what I felt like I needed in order to get to where I wanted to go."

Letting the data speak for itself

Alex Huth models language representation in the brain

"If you can get enough hours of data, enough data points, then we can let the data tell us what kind of features are important, instead of being forced to guess."

Alex Huth,
entering class of 2008

Alex Huth is an Assistant Professor of Computer Science and Neuroscience at the University of Texas at Austin. He combines approaches from neuroscience, computer science, mathematics, and linguistics to build complex models of how language and meaning is represented in the brain. He bases these models on large amounts of fMRI data about brain activity that he gathers as subjects listen to natural language — such as the autobiographical stories told in the podcast *The Moth*, which he used during his graduate work on language processing in **Jack Gallant's lab**. Gallant's research attracted Huth to Berkeley, and he did both his PhD and a postdoctoral fellowship in the Gallant lab. Huth joined the faculty at UT Austin along with his wife **Liberty Hamilton** (page 7) after going through the PhD Program together.

Huth says the program ". . . was really fantastic . . . our cohort was phenomenal. I'm still close friends with people from my cohort . . . I couldn't recommend it enough . . . Helen Wills is an extremely accepting place, people embrace their differences."

Revealing your brain

Erica Warp develops 'brain wearables'

"I think throwing fireballs with your mind in a game is cool, but taking care of the brain and helping the brain get stronger is what really motivates me."

Erica Warp,
entering class of 2006
Photo: Andrew Miller Photography

Erica Warp is the Vice President of Product at EMOTIV, where she develops wearable EEG products that allow monitoring of brain activity anywhere, for use by researchers and consumers alike. She's particularly interested in using the technology to improve health and wellness — for instance, helping people manage stress. At Berkeley, Warp studied neural development in **Ehud Isacoff's lab**. After earning her PhD, she founded an educational game company, Kizoom, to teach children about the brain. She is also an artist, and uses her creativity in her entrepreneurial ventures. Warp says that doing art allows her to "play with ideas in a non-linguistic way, which oftentimes opens up ideas that haven't been there. A lot of creativity is in connecting things that aren't obviously connected. A startup is a creative endeavor, a product is a creative endeavor, and research is a creative endeavor. Being able to let go of what you know and what connections are already well-established in your brain, and let those kind of sink down so that others can emerge, is a skill."

"Innately, I'm interested in trying to understand people and how they think and what their preferences are."

Chung-Hay Luk,
entering class of 2005

Making tech more user-friendly

Chung-Hay Luk researches how people interact with technology

As a user-experience (UX) researcher at Google, Chung-Hay Luk draws on her neuroscience and engineering backgrounds to study how technology can be improved to better meet people's needs.

Luk was an undergraduate bioengineering major at Berkeley, and then did her PhD in **Joni Wallis' lab** where she studied decision-making. For fun, she made clothing with embedded electronics, such as a skirt that changed color with movement, which she wore to the Berkeley Neuroscience annual retreats. After graduating, Luk's interests in technology and design led her to take a position at a brain training company, Posit Science, where she became interested in UX.

Luk now does UX research on Google's Photos product. When asked what she enjoys about her job, she says: "I've always liked people watching. If you study photography you can constantly do research. In fact, if I sit outside, there'd probably be somebody taking photos or struggling to share photos. It's been really nice because my research can go pretty much anywhere."

"Something we can really add to the field is being able to understand at a much higher level how sounds become meaningful words and concepts."

Liberty Hamilton,
entering class of 2008

Eavesdropping on the human brain

Liberty Hamilton records brain activity during neurosurgery to study processing of natural sounds

Liberty Hamilton is an Assistant Professor at the University of Texas at Austin in the departments of Communication Sciences and Disorders and Neurology. In collaboration with neurosurgeons, she uses electrocorticography (ECoG) to record directly from the cerebral cortex of patients undergoing epilepsy surgery to study how the brain processes and produces natural sounds like language.

As a graduate student, Hamilton studied sound representation in rodents with **Shaowen Bao** (now at the University of Arizona). She started working with patients during a postdoc with Edward Chang at UCSF. Now she uses ECoG and other techniques to study speech and language, and their development, in adults and children.

Reflecting on her time in the PhD Program, Hamilton says: "We had a lot of great opportunities to both talk about science but also *not* talk about science. I have very fond memories of the retreat — just getting to spend time with other grad students and have people going through the same experience . . . I felt like all of them had my back."

Read full versions of alumni profiles on our website:
neuroscience.berkeley.edu/tag/alumni-profile/

Honors and Awards

Kristin Scott, Professor of Molecular and Cell Biology, was elected to the American Academy of Arts and Sciences. She studies taste detection in fruit flies to understand how sensory processing can give rise to specific behaviors.

Christopher Chang, Professor of Chemistry and Molecular and Cell Biology, Class of 1942 Chair, and Howard Hughes Medical Institute Investigator, was awarded the 2019 Raymond and Beverly Sackler International Prize in Chemistry from Tel Aviv University. His research is focused on inorganic, organic, and biological chemistry, including the role of metals in the nervous system.

Ke Xu, Assistant Professor of Chemistry and Chan Zuckerberg Biohub Investigator, received a NIH Director's New Innovator Award for his work developing tools to study biological processes on the nanoscale.

Helen Bateup, Assistant Professor of Neurobiology, was appointed as a Chan Zuckerberg Biohub Investigator. Her research focuses on the molecular basis of synapse and circuit changes associated with epilepsy and autism.

Markita Landry, Assistant Professor of Chemical and Biomolecular Engineering, received a 2018 DARPA Young Faculty Award for her work developing optical probes for neuromodulators such as dopamine.

Lucia Jacobs, Professor of Psychology, won a 2018-2019 Radcliffe Institute Fellowship from Harvard University's Radcliffe Institute for Advanced Study. Her research is focused on cognitive strategies and olfactory cues for spatial navigation in changing environments.

David Schaffer, Professor of Chemical and Biomolecular Engineering, was selected as a Bakar Fellow. He also won an Intercampus Research Award from the Chan Zuckerberg Biohub to collaborate with researchers from UCSF and Stanford to develop tools to study the interactions between neuroimmune and other brain cells in humans.

Stephan Lammel, Assistant Professor of Neurobiology, won the 2019 C.J. Herrick Award in Neuroanatomy from the American Association of Anatomists. He studies midbrain dopamine circuits in reward-based behaviors and pathological changes in addiction, depression, and schizophrenia.

Frédéric Theunissen, Professor of Psychology, received a Carl Friedrich von Siemens Research Award from the Alexander von Humboldt Foundation in recognition of his work on the perception of complex sounds.

Linda Wilbrecht, Associate Professor of Psychology, won a Winter 2019 Pilot Award from the Simons Foundation Autism Research Initiative, for a project entitled: "The influence of autism risk genes on reinforcement learning and corticostriatal circuit development."

Polina Kosillo, a postdoctoral fellow in the Bateup lab, was awarded a NARSAD Young Investigator Grant to study the role of mTORC1 signaling in dopamine release, which may be involved in dopamine-related disorders such as ADHD, autism spectrum disorders, and anxiety.

PhD Program students, entering class of 2018.
Top row: Matt Davis, Erin Aisenberg, Marisa Becerra, Julia Bleier, Brett Nelson, Mark Gorenstein
Bottom row: Katie Cording, Madeline Klinger, Sonali Mali, Azure Grant

Ways to give

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