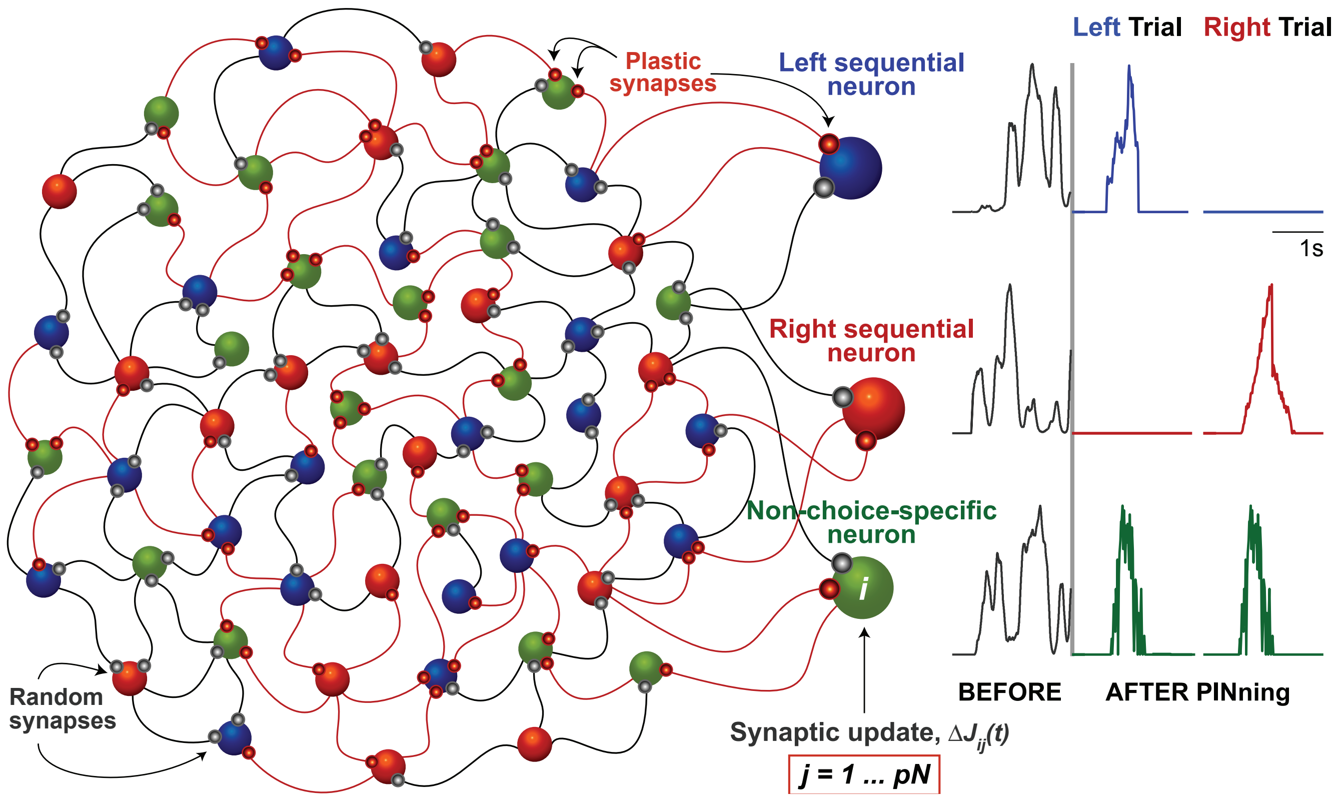
SPRING 2020

Icahn School of Medicine at Mount Sinai

The Friedman Brain Institute



Schematic of a simulated neural network for implementing working memory. Rajan et al., Neuron, 2016

Building Predictive Models of Brain Health and Disease

The past few decades have seen a revolution in how we study the brain. It was not long ago when we first observed the activity of dozens of neurons at a time in a single part of the brain of an awake, behaving animal. Now, we can record the activity of many hundreds, even thousands, of neurons simultaneously across many different brain areas while memories are being formed or emotions experienced, allowing us to understand the brain in normal function, what goes wrong when it fails in psychiatric and neurological disorders, and potentially how these flaws might be corrected. However, making sense of all of this data (petabytes) requires a completely new approach to how we study the brain, an effort known as computational neuroscience.

Today, our scientists are able to use machine learning strategies to analyze the immense data from their neuroscience experiments and then build models that can be used to make predictions about how the brain works in both health and disease. Some of this work is being carried out under the auspices of Mount Sinai's new Lipschultz Center for Cognitive Neuroscience.

The laboratory of **Kanaka Rajan, PhD**, who joined Mount Sinai two years ago from Princeton University, has been at the forefront of developing predictive computational models to understand how neurons, ensembles of neurons, and whole brain areas interact during cognition and emotion. With these models, the Rajan laboratory has determined how neural circuits become dysfunctional in anhedonic-like states, providing unique insight into the basis of depression.

Another innovative use of computational neuroscience is to understand how circuits in the brain support decision-making. **Erin Rich, MD, PhD**, who received both degrees from Mount Sinai before completing a postdoctoral fellowship at UC Berkeley, uses state-of-the-art neurophysiology methods to record the activity of hundreds of neurons in the prefrontal cortex while monkeys make preference-based decisions. Computational techniques predict which options will be chosen based on neural activity, allowing Dr. Rich and her team to study the evolution of a decision with millisecond-level precision.

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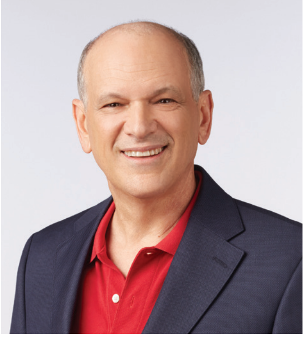
MESSAGE FROM THE DIRECTOR



Eric J. Nestler, MD, PhD
Nash Family Professor of Neuroscience; Director, The Friedman Brain Institute; Dean for Academic and Scientific Affairs, Icahn School of Medicine at Mount Sinai

Artificial intelligence (AI)—and its promise to transform our understanding of the brain and treatment of brain disorders—is the focus of this newsletter. AI, which includes machine learning or deep learning, describes a machine simulating the learning and problem-solving capabilities of the human brain. Some believe that true AI, where machines operate completely by themselves as depicted in *The Terminator*, *Westworld*, and *Ex Machina*, for example, does not yet exist and that we are currently in an age of "augmented intelligence," where humans use computers to boost their work. That may be a more accurate term.

Mount Sinai has been a leader in the application of AI to medicine. We recently created the Center for Artificial Intelligence and Human Health, the BioMedical Engineering and Imaging Institute, and the Hasso Plattner Institute for Digital Health at Mount Sinai. Each of these entities is driving scientific and medical advances in the areas of genomics, imaging, electronic health records, and digital data. Mount Sinai will continue to invest resources in these AI efforts, with a major focus on the nervous system.

In this issue, we explain the applications of AI to help us understand how the brain works in health and disease, a field called computational neuroscience. We also highlight ways in which AI is being used to better diagnose brain disease, an effort that is already improving care for patients.

mountsinai.org/fbi *http://labs.neuroscience.mssm.edu/project/nestler-lab/* *@EricJNestler*

› BUILDING PREDICTIVE MODELS OF BRAIN HEALTH AND DISEASE *continued from page 1*

A specific type of computational model, known as a reinforcement-learning model, which allows for "learning" through repeated experience, is now widely used in industry and has been impactful in neuroscience.

The laboratory of **Peter Rudebeck, PhD**, uses several varieties of reinforcement-learning models to predict how monkeys learn while they are in situations that are uncertain and noisy. The goal of this research is to reveal the contribution of specific circuits in the brain to learning and how these circuits are altered in psychiatric illness. Dr. Rudebeck completed his training at Oxford University and the National Institutes of Health.

Memory decline—either through normal or pathological aging—is an increasing burden in society. The laboratory of **Denise Cai, PhD**, uses advanced computational techniques to aid her research focused on the basis of memory in the course of normal and pathological aging. Her laboratory uses miniature microscopes—which were co-developed with colleagues at the University of California, Los Angeles (UCLA) and the Icahn School of Medicine at Mount Sinai—to study the activity of hundreds of neurons simultaneously in the brains of mice, as important events are experienced, learned, and later remembered and retrieved.

The laboratory of **Tristan Shuman, PhD**, is applying computational neuroscience to reveal how epileptic seizures change the patterns of neural activity that are engaged during cognition. The objective is to determine how this pathological activity might be corrected. Here, computational approaches are essential to identifying aberrant patterns of neural activity that would then trigger corrective neurostimulation to reduce seizure activity and restore normal cognitive function. Both Drs. Cai and Shuman joined Mount Sinai from UCLA in 2017.

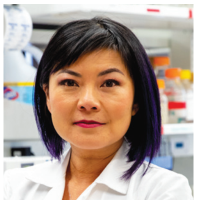
Computational models can also be used to better understand the cognitive and affective processes that become dysfunctional in humans with psychiatric disorders. In 2018, **Xiaosi Gu, PhD**, one of the foremost experts on computational psychiatry, joined Mount Sinai from The University of Texas at Dallas. Along with colleagues, she is developing ways to computationally model craving and what heightens craving in people with drug addiction in efforts to predict, and ultimately prevent, relapse.

Daniela Schiller, PhD, and her laboratory similarly use computational methods to better understand the processes that become dysfunctional in veterans with post-traumatic stress disorder (PTSD). Working with the Department of Veterans Affairs, Dr. Schiller and co-workers are developing computational models to further characterize how fear- and safety-learning are both altered in veterans with PTSD, an effort to improve treatments.

Kanaka Rajan, PhD, Assistant Professor, Neuroscience

Erin Rich, MD, PhD, Assistant Professor, Neuroscience

Peter Rudebeck, PhD, Associate Professor, Neuroscience, and Psychiatry



Denise Cai, PhD, Assistant Professor, Neuroscience

Tristan Shuman, PhD, Assistant Professor, Neuroscience

Xiaosi Gu, PhD, Assistant Professor, Psychiatry, and Neuroscience

Daniela Schiller, PhD, Associate Professor, Psychiatry, and Neuroscience

Artificial Intelligence in the Neurosciences Intensive Care Unit

Anthony Costa, PhD, Assistant Professor, Neurosurgery

Neha Dangayach, MD, MSCR, Assistant Professor, Neurosurgery, and Neurology

Eric K. Oermann, MD, Instructor, Neurosurgery

Mount Sinai is developing a new kind of intensive care unit (ICU) telemetry for the brain using deep learning as part of its mission to re-imagine the most basic aspect of the clinical neurosciences: how to best observe and interpret brain diseases at the bedside. Neurological examination by clinicians and scientists remains the primary tool for assessing brain function based on observed behavior and other findings (vision and sensation, for example). Such assessments, however, can demonstrate a high degree of variability among observers and are often captured at a low sampling rate (hourly at most). This subjective, slow, observer-dependent phenotyping is at odds with the rapidly expanding high-throughput methods for data collection and analysis in other fields.

Physicians and scientists are in the process of aggregating the tremendous amounts of data being generated on each patient by the Neurosciences Intensive Care Unit (NSICU) into a single, novel telemetry signal for brain function that can be used by neurosurgeons and other clinicians to track and guide the treatment of patients. The newly created "smart" NSICU—which opened in October 2019 and is located on an entire floor of The Mount Sinai Hospital—is leveraging novel tools for continuous time-series analysis being developed by a multidisciplinary team including neurosurgeons, neurologists, basic neuroscientists, and data scientists. The novel telemetry signal will be used to assist in the care and treatment of the sickest and most vulnerable patients, as well as help to redefine how to assess their conditions. This effort is being driven by **Anthony Costa, PhD**; **Neha Dangayach, MD, MSCR**; **Eric K. Oermann, MD**; and **Kanaka Rajan, PhD**.

A Transformational Approach to Neuropathology

John Crary, MD, PhD, Professor, Pathology, Molecular and Cell-Based Medicine; and Neuroscience

Jack Zeineh, MD, Chief Technology Officer, Center for Computational and Systems Pathology

Gerardo Fernandez, MD, Associate Professor, Pathology, Molecular and Cell-Based Medicine

The application of artificial intelligence to medicine promises to be profoundly disruptive, transforming all specialties. One place where this is beginning to play out is in the microscopic assessment of brain tissues in the clinical neuropathology laboratory. Historically, this has been slow, imprecise, and poorly reproducible, requiring the experience of a highly trained specialist, such as a neuropathologist, to review slides and issue diagnostic opinions—a subjective process likened to "reading the tea leaves" on a cellular level. In 2019, **John Crary, MD, PhD**, in collaboration with the Center for Computational and Systems Pathology, led by **Jack Zeineh, MD**, and **Gerardo Fernandez, MD**, published the first paper on the results of deploying a form of deep machine learning, a computational approach involving training convolutional neural networks to create a classifier capable of recognizing and quantifying pathological changes from digital images of brain tissue slides from patients with neurodegenerative diseases. They chose to focus on neurofibrillary tangle pathology, which has distinctive features that allow differentiation of Alzheimer's disease, normal aging, chronic traumatic encephalopathy that is induced by traumatic brain injury, parkinsonism, and other conditions. The team now has additional funding from the Rainwater Charitable Foundation/Tau Consortium and The Michael J. Fox Foundation to build additional neural networks capable of rapid and reproducible analyses of slides and discovery of new cellular indicators of neurodegeneration.

New Election to National Academy of Medicine

Rachel Yehuda, PhD, a world-renowned researcher whose discoveries have revolutionized the study and treatment of post-traumatic stress disorder (PTSD), was elected in 2019 to the National Academy of Medicine (NAM), the nation's highest honor for medical researchers. Dr. Yehuda is Professor and Vice Chair for Veterans Affairs for the Department of Psychiatry, Professor of Neuroscience, and Director of the Traumatic Stress Studies Division at the Icahn School of Medicine at Mount Sinai. Dr. Yehuda's laboratory, which includes the PTSD Clinical Research Program at the James J. Peters Veterans Affairs Medical Center, focuses on trauma, PTSD, and resilience. Her election brings the number of Friedman Brain Institute (FBI) faculty who are NAM members to eight, a major distinction for Mount Sinai's neuroscience community. Other NAM members from the FBI are: Joseph D. Buxbaum, PhD; Dennis S. Charney, MD; Kenneth L. Davis, MD; Alison M. Goate, DPhil; Yasmin Hurd, PhD; Eric J. Nestler, MD, PhD; and Barbara G. Vickrey, MD, MPH.

Rachel Yehuda, PhD

2020 Friedman Brain Institute Research Scholars

This unique effort, funded entirely through philanthropy, supports innovative and collaborative pilot brain research at Mount Sinai, giving our most promising researchers the ability to explore bold new ideas aimed at accelerating diagnostic and therapeutic discoveries.

Mount Sinai Research Scholar Award
Roger Clem, PhD, and Paul Slesinger, PhD
"Neuropeptide signaling by prefrontal interneurons in fear memory encoding"

Karen Strauss Cook Research Scholar Award
Ana Pereira, MD, and John F. Crary, MD, PhD
"Single cell mapping of tau pathology in the degenerating human brain"

Joseph and Nancy DiSabato Research Scholar Award
Minghui Wang, PhD, and Aiqun Li, PhD
"Multiplex identification of novel microglia targets of Alzheimer's disease using CRISPRa and scRNA-seq"

Dyal Research Scholar Award
Kanaka Rajan, PhD; Neha Dangayach, MD, MSCR; and Eric K. Oermann, MD
"Unlocking critical care data to predict catastrophic clinical events using artificial intelligence"

Fascitelli Research Scholar Award
Silvia De Rubeis, PhD, and Zhuhao Wu, PhD
"Capture the cellular and molecular drivers of cortical development in DDX3X syndrome"

Richard and Susan Friedman Research Scholar Award
Manish Jha, MBBS; Priti Balchandani, PhD; Scott Russo, PhD; and James Murrough, MD, PhD
"Using high-field neuroimaging to unlock the therapeutic potential of orexin antagonists for depressed patients with anger and irritability"

Katz / Martin Scholar Award
Lotje Dorothee de Witte, MD, PhD; and Viviana Simon, MD, PhD
"Dissecting the mechanisms driving microgliosis in primary human microglia cells"

Lipschultz Scholar Award
Abha Karki Rajbhandari, PhD, and Ivan de Araujo, PhD
"Regulation of PTSD via neuropeptidergic signaling in the brain-vagus-body axis"

Nash Family Research Scholar Award
Allison Waters, PhD; James Murrough, MD, PhD; and Helen S. Mayberg, MD
"Ketamine plus deep brain stimulation for severe treatment-resistant depression: identifying synergistic brain mechanisms to advance novel treatment discovery"

Satter Research Scholar Award
Dolores Malaspina, MD, MS, MSPH; and Yuen Ping Toco Chui, PhD
"Psychosis insights from ocular imaging"

Shah Research Scholar Award
Tristan Shuman, PhD, and Yasmin Hurd, PhD
"Neural circuit mechanisms driving therapeutic effects of CBD in epileptic mice"

Sundaram Research Scholar Award
Bojan Losic, PhD; Alex Charney, MD; and Navneet Dogra, PhD
"Live brain profiling via blood-derived exosomal small RNA"

Zhao Research Scholar Award
Coro Paisán-Ruiz, PhD; Joanna Jen, MD, PhD; and Robert Sebra, PhD
"Mapping the genomic landscape of episodic ataxias"

The Scholars represent the departments of Cell, Developmental and Regenerative Biology; Diagnostic, Molecular and Interventional Radiology; Genetics and Genomic Sciences; Medicine; Microbiology; Neurology; Neuroscience; Neurosurgery; Otolaryngology; Ophthalmology; Pathology; and Psychiatry.

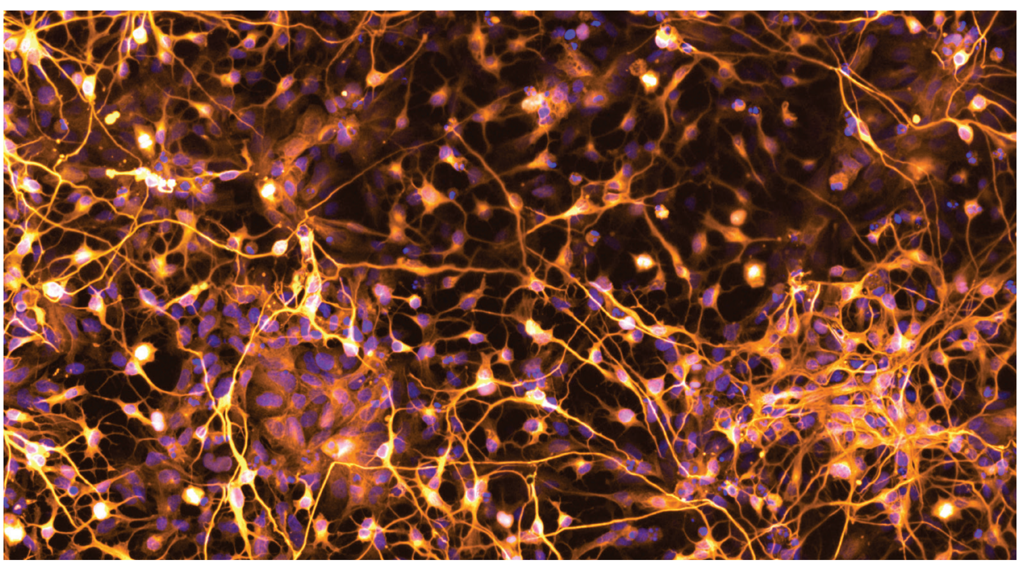


PHOTO ESSAY

Golden Neurons

Plexin-B2-mediated cell-intrinsic stiffness leading to spontaneous neuronal differentiation upon neural induction. β-III tubulin (TUJ1; gold) and DAPI (blue).

Credit: Image courtesy of Chrystian Junqueira Alves, PhD, Nash Family Department of Neuroscience

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