Mount Sinai

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MOUNT SINAI SCHOOL OF MEDICINE

THE FRIEDMAN BRAIN INSTITUTE

COMPASSIONATE CARE, PIONEERING RESEARCH

The Friedman Brain Institute is one of the world's premier institutions dedicated to advancing our understanding of brain and spinal cord disorders, and driving innovative approaches to new treatments and diagnostic tests, through translational research.

FALL 2012

INSIDE THIS ISSUE

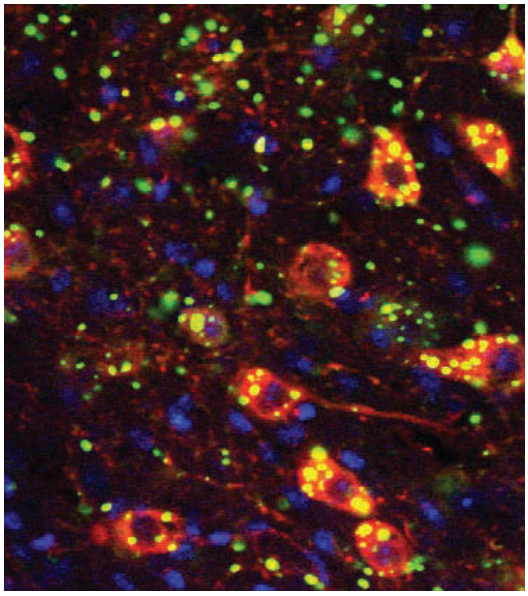
Millions of Americans have movement disorders, a heterogeneous collection of severe and debilitating illnesses. The most common is Parkinson's disease, which is caused by the death of midbrain dopamine neurons and other nerve cells in the brain. Current treatments, like L-Dopa, are effective at treating motor abnormalities during earlier stages of the illness, but they eventually lose effectiveness. Dystonias are characterized by painful, involuntary contractions of muscles, often involving the head and neck. Huntington's disease and amyotrophic lateral sclerosis (ALS, commonly referred to as Lou Gehrig's disease) are other devastating movement disorders.

Mount Sinai has become a leading research and clinical center for movement disorders—in particular, Parkinson's disease and dystonias. Melvin Yahr, MD, who became Chair of Mount Sinai's Department of Neurology in 1974, helped establish the use of L-Dopa. Under the subsequent leadership of C. Warren Olanow, MD, and current Chair Stuart C. Sealfon, MD, the Neurology department has led research into the use of cell transplantation and viral gene therapy for Parkinson's disease, and pioneered the use of deep brain stimulation. Mount Sinai faculty also helped establish the use of botulinum toxin for the treatment of dystonias and identified several genes responsible for hereditary forms of the illness, and we are world-renowned for our special expertise in treating movement disorders in musicians.

The Friedman Brain Institute (FBI) is maintaining this position of excellence with the support of our outstanding faculty and the recruitment of several new leaders in the field. While treatment of movement disorders remains challenging, the last decade has witnessed tremendous advances in our understanding of these illnesses, both their underlying neurobiology and genetics. This publication provides an overview of our efforts in these conditions and it is our expectation that continued discoveries of disease mechanisms will lead to more effective treatments and, ultimately, cures during the next decade.

WWW.MOUNTSINAI.ORG/FBI

Eric J. Nestler, MD, PhD
Nash Family Professor and Chair,
Department of Neuroscience,
Director, The Friedman Brain Institute
eric.nestler@mssm.edu
http://neuroscience.mssm.edu/nestler



RESEARCH FRONTIERS

Deciphering the Biological Basis of Movement Disorders

Most movement disorders, including Parkinson's disease (PD), essential tremor (ET), and dystonia, have both genetic and environmental components. The familial forms of the illnesses have been more intensely investigated because dissection of the disease mechanisms becomes tractable once the causative genes have been identified. Discovery of the disease genes sets the stage for modeling disease pathophysiology in animals, making it possible to design new treatment strategies against validated drug targets.

(continued on page 2)

Figure 1. Protein aggregates induced by lack of autophagy function. The Yue Laboratory has genetically knocked out in mice proteins required for autophagy. The result is a dramatic increase in intracellular aggregates (green) within both dopaminergic neurons (red, marked by tyrosine hydroxylase) and non-dopaminergic neurons (unlabeled) (blue marks all cell nuclei). Image prepared by Lauren Friedman, a neuroscience graduate student from the Yue Laboratory

Deciphering the Biological Basis of Movement Disorders (continued from page 1)

Two FBI scientists have been pioneers in searching for genetic factors that cause movement disorders: Coro Paisán-Ruiz, PhD, Assistant Professor of Neurology, Genetics and Genomic Sciences, and Psychiatry, who has discovered several genes for PD, early-onset parkinsonian-like syndromes, and ET; and Laurie Ozelius, PhD, Associate Professor of Genetics and Genomic Sciences, and Neurology, whose laboratory has identified three genes for dystonia and is working to find others.

Both work closely with Steven Frucht, MD, and his team at the Robert and John M. Bendheim Parkinson's and Movement Disorders Center (see page 3) to recruit patients, collect DNA, and employ state-of-the-art molecular tools available through Mount Sinai's new Institute for Genomics and Multiscale Biology. These novel technologies enable researchers to rapidly discover new mutations, even in circumstances where conventional approaches have failed.

In related work, Chenjian Li, PhD, Associate Professor of Neurology, and Zhenyu Yue, PhD, Associate Professor of Neurology, and Neuroscience, have developed animal models for PD with mutations linked to the most common known genetic cause of PD, a gene that encodes a protein called LRRK2 (leucine-rich repeat kinase 2). Mutations in LRRK2 account for approximately 2 percent of all sporadic cases of PD among Caucasians, and about 20 percent of all such cases among Ashkenazi Jews, and 40 percent of North African Berber Arab patients. The most prevalent mutation causes a neurotoxic "gain of function" potentially through an aberrant increase in LRRK2's kinase activity. Dr. Li is a leading expert in developing new genetic tools, including mice and rats that express human mutations of LRRK2 or other disease genes, which are widely used in more than 400 academic and industry laboratories around the world. Dr. Li's group has also established mouse and rat models for Huntington's disease (HD), another movement disorder, and is piloting the development of such models in non-human primates where human brain pathology is reproduced to a far greater extent than in rodents.

In addition to investigating how LRRK2 mutations lead to the death of midbrain dopamine neurons in PD, Dr. Yue's laboratory is researching possible biomarkers and therapeutic strategies to block LRRK2 pathogenic kinase activity using his preclinical PD models. Dr. Yue is also a pioneer in studies of autophagy, a ubiquitous, cellular "self-eating" process critical for survival, during which cellular debris is brought to lysosomes for degradation. There is increasing evidence that many neurodegenerative diseases, including PD and HD, have defects in autophagy, which allows the accumulation of toxic protein aggregates within vulnerable neurons, leading to their ultimate demise (see Figure 1). The Yue Laboratory has played a leading role nationally in defining the molecular pathways that control autophagy within neurons, with the aim of developing autophagy-enhancing drugs to treat neurological disorders.

The ultimate goal of this uniquely broad-based, multidisciplinary research, which is tightly aligned with clinical efforts, is to generate a comprehensive understanding of these disorders at the genetic, cellular, circuitry, and behavioral levels, so that better diagnostic tests, treatments, and, ultimately, cures can be developed.

Coro Paisán-Ruiz, PhD
Assistant Professor of Neurology, Genetics and Genomic Sciences, and Psychiatry
coro.paisan-ruiz@mssm.edu

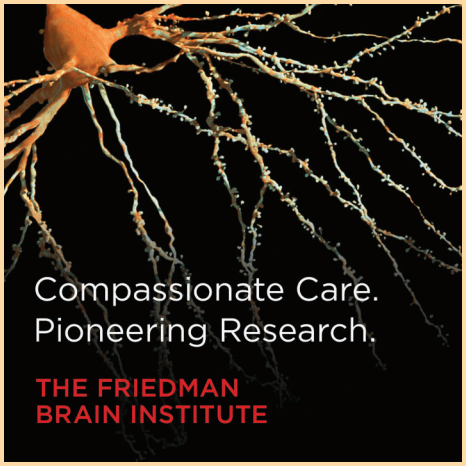
Laurie J. Ozelius, PhD
Associate Professor of Neurology, and Genetics and Genomic Sciences
laurie.ozelius@mssm.edu

Chenjian Li, PhD
Associate Professor of Neurology
chenjian.li@mssm.edu

Zhenyu Yue, PhD
Associate Professor of Neurology, and Neuroscience
zhenyu.yue@mssm.edu

PHILANTHROPY

Major Gifts, Generous Support for The Friedman Brain Institute



A $5.25 million gift from the estate of Robert A. Bendheim, who served as a member of the Mount Sinai Boards of Trustees for more than 50 years, will advance The Friedman Brain Institute's leadership in movement disorders care and research. The gift will support recruitment as well as capital improvements to laboratories focusing on movement disorders. Mr. Bendheim was a devoted advocate for movement disorders research.

Mr. Marc S. Lipschultz, who joined Mount Sinai's Boards of Trustees in 2010, made a gift to The Friedman Brain Institute that will support a range of strategic priorities, including faculty recruitment and ongoing research projects. "The Friedman Brain Institute is setting the pace for the discovery of revolutionary new therapies for brain disease," said Mr. Lipschultz. "I hope to help accelerate that momentum."

In addition to numerous grants from the National Institutes of Health, Mount Sinai's research programs in movement disorders also benefit from generous funding from the Michael J. Fox Foundation (https://www.michaeljfox.org/) and the Bachmann-Strauss Dystonia & Parkinson Foundation (http://www.dystonia-parkinsons.org/), among others.

Innovative Treatments for Movement Disorders

The newly renovated Robert and John M. Bendheim Parkinson's and Movement Disorders Center serves as the foundation for the Department of Neurology's Movement Disorders Division and continues to further Mount Sinai's reputation for clinical, research, and educational excellence in the field.

Clinicians, led by Division Director Steven Frucht, MD, Professor of Neurology, provide comprehensive evaluation and care to the full spectrum of patients with movement disorders, including Parkinson's disease and related parkinsonian-like syndromes, dystonia, tremor, chorea, myoclonus, cerebellar ataxias, and pediatric movement disorders, among others.

The center is a leader in the field of deep brain stimulation (DBS) surgery for the treatment of Parkinson's disease, tremor, and dystonia, and is now one of the busiest referral sites for DBS surgery in North America. It is also on the cutting edge of new approaches and techniques for surgery that optimize patient comfort and safety. Figure 1 illustrates the placement of a stimulating electrode in the subthalamic nucleus of a patient with Parkinson's disease, a treatment that has transformed the lives of thousands of patients. Other ongoing clinical trials currently involve novel agents for motor fluctuations and dyskinesias in Parkinson's disease, and new botulinum toxin preparations for focal dystonias. The center is led by co-directors Barbara Kelly Changizi, MD, Assistant Professor of Neurology, and Brian Kopell, MD, Associate Professor of Neurosurgery, Neuroscience, Psychiatry, and Neurology.

The movement disorders team is also pioneering a multidisciplinary approach to research. Center clinicians collaborate closely with geneticists Laurie Ozelius, PhD, and Coro Paisán-Ruiz, PhD, both leaders in the discovery of genes responsible for familial forms of dystonia and parkinsonism. Because most forms of dystonia display reduced penetrance (not everyone with the disease gene develops the illness), Dr. Ozelius works closely with Kristina Simonyan, MD, PhD, Assistant Professor of Neurology, and Otolaryngology, on characterizing MRI-based and other endophenotypes for dystonia. Dr. Simonyan is regarded as a world authority on functional neuroimaging of dystonia. Additionally, Dr. Paisán-Ruiz's team is examining the function of movement disorder genes in the zebrafish nervous system, while Dr. Ozelius also collaborates with Michelle Ehrlich, MD, Professor of Neurology, Pediatrics, and Genetics and Genomic Sciences, on mouse models of dystonia.

Through Mount Sinai's Institute for Personalized Medicine, patients are actively enrolled in a genetic database that allows investigators to search for new genes responsible for inherited forms of these disorders. Projects are under way to investigate the central nervous system mechanisms of spasmodic dysphonia, an unusual and often debilitating form of dystonia affecting the voice. Experimental treatments are being explored for this condition based on an improved understanding of its neural and circuit mechanisms (see Figure 2).

One of the central missions of the Movement Disorders Division is to train the next generation of academic clinician-scientists. Each year, the fellowship program allows two neurologists who have completed residency training to obtain expertise in the clinical care of movement disorder patients, and to take advantage of the clinical and research opportunities within the Mount Sinai community to launch their academic careers. The center also provides training and education in these areas for residents, medical students, and visiting observers from throughout the world. Our continuing medical education activities, patient outreach initiatives, and lectureships at major academic meetings also ensure that the Center's activities reach a national and international audience.

Steven Frucht, MD
Director, Department of Neurology
Movement Disorders Division,
Professor of Neurology
steven.frucht@mssm.edu

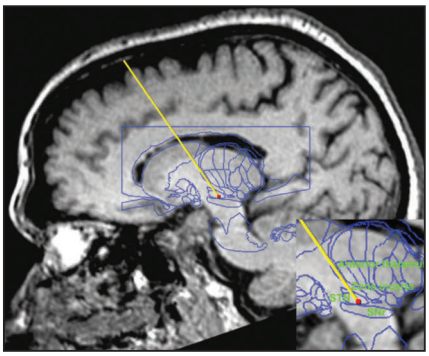


Figure 1. Microelectrode targeting the subthalamic nucleus in a patient with Parkinson's disease is shown on this MRI (magnetic resonance imaging) scan. Mount Sinai is the only center in New York State that combines microelectrode recording with intra-operative imaging, allowing more accurate and safer surgical treatment. Figure courtesy of Brian Kopell, MD

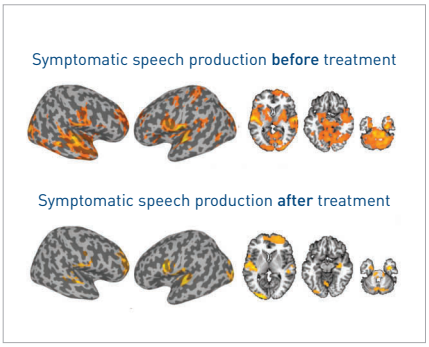


Figure 2. Functional MRI of a patient with spasmodic dysphonia (dystonia affecting the vocal cords) shows widespread abnormal activation (yellow) in both cortical and subcortical areas. After treatment with the novel drug sodium oxybate (Xyrem), abnormal activation is substantially reduced, correlating with clinical improvement. Figure courtesy of Kristina Simonyan, MD, PhD

Robert and John M. Bendheim Parkinson's and Movement Disorders Center

Steven Frucht, MD
Director, Professor of Neurology

Barbara Kelly Changizi, MD
Assistant Professor of Neurology

Catherine Cho, MD
Assistant Professor of Neurology

Brian Kopell, MD
Associate Professor of Neurosurgery, Neuroscience, Psychiatry, and Neurology

C. Warren Olanow, MD
Professor of Neurology, and Neuroscience

Winona Tse, MD
Assistant Professor of Neurology

Miodrag Velickovic, MD
Assistant Clinical Professor of Neurology

Ruth Walker, MD, PhD
Associate Professor of Neurology

MOUNT SINAI SCHOOL OF MEDICINE
THE FRIEDMAN BRAIN INSTITUTE
ONE GUSTAVE L. LEVY PLACE, BOX 1107
NEW YORK, NY 10029-6574

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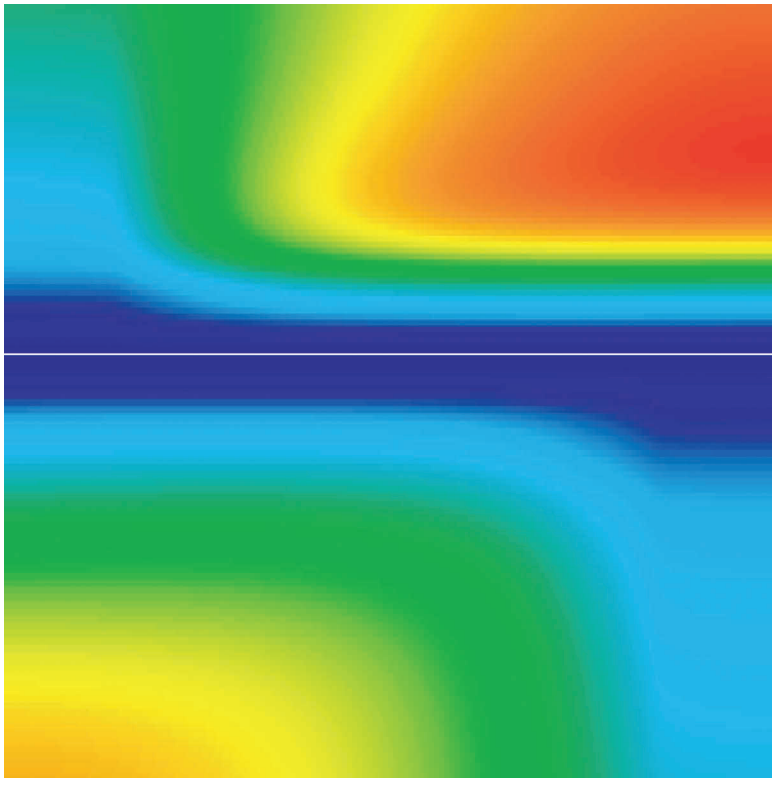
PHOTO ESSAY

Graphical Representations (Kymographs) of the Synthesis of Cyclic AMP



Graphical representations (kymographs) of the synthesis of cyclic AMP, a second messenger induced within neurons by the neurotransmitter norepinephrine, based on mathematical models. The images represent length of the neuron's dendrite on the horizontal axis, varying time on the vertical axis, and the different colors represent varying concentrations of cyclic AMP. Figure courtesy of Susana Neves, PhD, and Ravi Iyengar, PhD

Susana Neves, PhD
Assistant Professor, Pharmacology and Systems Therapeutics
susana.neves@mssm.edu

Srinivas (Ravi) Iyengar, PhD
Professor and Chair, Pharmacology and Systems Therapeutics and Director of the Experimental Therapeutics Institute
ravi.iyengar@mssm.edu