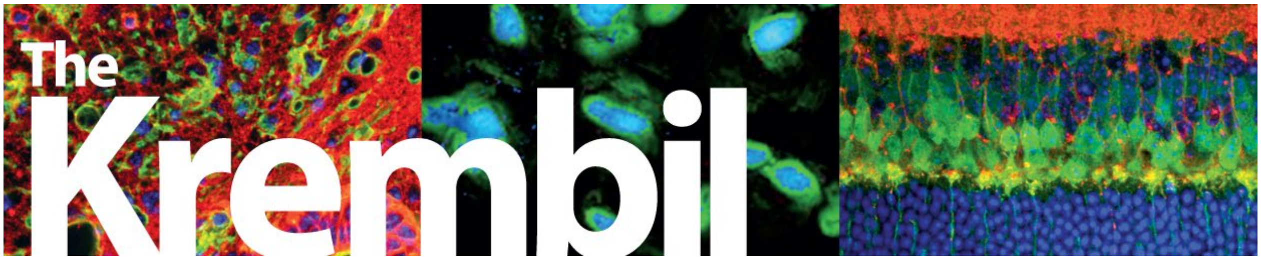


March 2023

The Krembil is the official newsletter of the Krembil Research Institute. It informs the Toronto Western Hospital community, external stakeholders and interested community members about exciting news and innovative research happening at the Krembil Research Institute.

Stories in this month's issue:

Jaideep Bains, PhD
Director, Krembil Research Institute
University Health Network

News

Science is for Everyone

Krembil highlights some of its talented women researchers and health care providers.

(L-R) Mary Ito, Dr. Karen Davis, Amina Adama and Laura Passalent.

In celebration of the *International Day of Women and Girls in Science*, the Krembil Research Institute hosted a free livestream event on February 10, 2023.

Over 4000 people watched the event live, which can be viewed here.

Moderated by CBC host Mary Ito, the livestream featured the following three Krembil researchers and health care providers:

● Dr. Karen Davis, Senior Scientist, Krembil Brain Institute;

● Amina Adama, PhD Candidate, Donald K. Johnson Eye Institute; and

● Laura Passalent, Advanced Practice Physiotherapist and Clinician Investigator, Schroeder Arthritis Institute

Each speaker gave a short, TED-style talk about their life and career path, and what inspired them to enter their field. Topics included the use of brain imaging techniques to study chronic pain; potential treatments for glaucoma and other retinal diseases; and holistic physiotherapy for patients living with arthritis.

The livestream also featured a guest appearance from the Honourable Marci Ien, Canada's Minister for Women and Gender Equality and Youth, who shared an inspiring message about the power of education.

Addressing young people around the world, Marci said, "Follow your passion, unapologetically. Seek and give mentorship wherever you can because, with that, comes many invaluable lessons and resources. The power that comes from working hard and working together is limitless."

The event concluded with a panel discussion in which the speakers answered questions submitted by classrooms in and outside of Ontario—one that came from as far away as Zimbabwe.

Want more inspiring stories about women researchers at UHN? Watch this short video.

According to the United Nations Educational, Scientific and Cultural Organization (UNESCO), women account for only 33% of researchers worldwide, despite representing nearly half of undergraduate and graduate students. To address gender inequities in science, technology, engineering and math (STEM) fields, the United Nations declared February 11 as the International Day of Women and Girls in Science.

Season 2: Your Complex Brain

Your Complex Brain continues to shine a light on groundbreaking brain research from UHN.

On March 21, 2023, tune in for Season 2 of the Krembil Brain Institute's podcast *Your Complex Brain*.

Hosted by Heather Sherman, Manager of Communications for the Krembil Brain Institute, this educational podcast is geared towards a general audience and is freely available on all major podcast platforms, including Apple Podcasts, Spotify and Google Podcasts. New episodes will air every other Tuesday.

Listeners will enjoy in-depth interviews with leading neuroscientists and clinicians from the Krembil Brain Institute, as well as moving personal accounts of brain injury, disease and recovery from patients and dedicated care teams.

The podcast will also shine a light on some of the Institute's talented trainees and its collaborations with national and international researchers and advocacy organizations that enable world-class discoveries and clinical innovations.

Season 2 will explore a wide range of brain-related topics, including:

- a new theory of Alzheimer disease;
- how the brain responds to pain;

● how gender affects the diagnosis of brain disease; and
● the future of deep brain stimulation

To learn more, watch the Season 2 trailer here.

"This podcast is such a great way to connect with our community partners and members of the public, to let them know about the amazing science happening at the Krembil Brain Institute, and what makes us a world leader in brain research and care," says Krembil Director Dr. Jaideep Bains.

With more than 14,000 downloads for its first season, *Your Complex Brain* was a finalist for the *Canadian Online Publishing Awards 2022 Best Podcast* award.

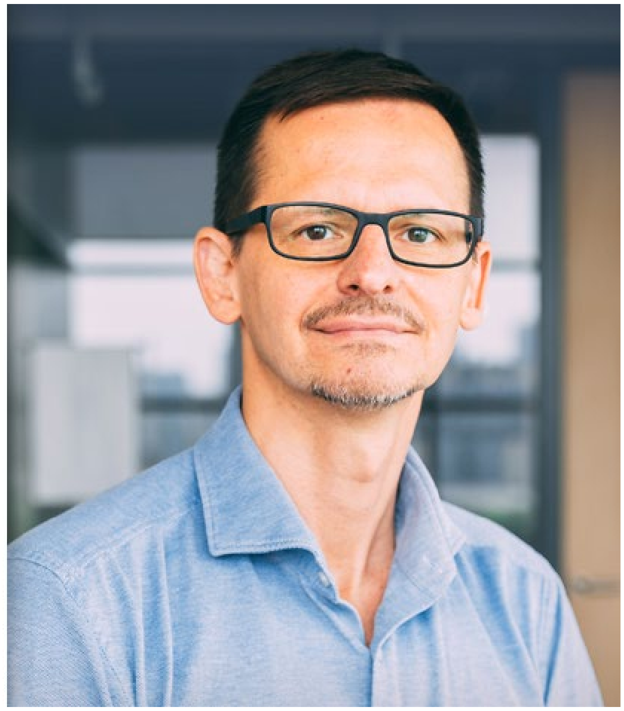
The Krembil Brain Institute is home to one of the world's largest and most comprehensive teams of scientists and clinicians dedicated to developing treatments for diseases of the brain and spine. This podcast celebrates the work of this exceptional multidisciplinary team and breaks down barriers between scientists and the public.

For more information about the podcast, visit https://www.uhn.ca/Krembil.

Research

Protein Misfolding and Disease

The ability of misfolded proteins to spread in the brain explains Lewy body disorder symptoms.

(L-R) Drs. Ivan Martinez-Valbuena and Gabor Kovacs.

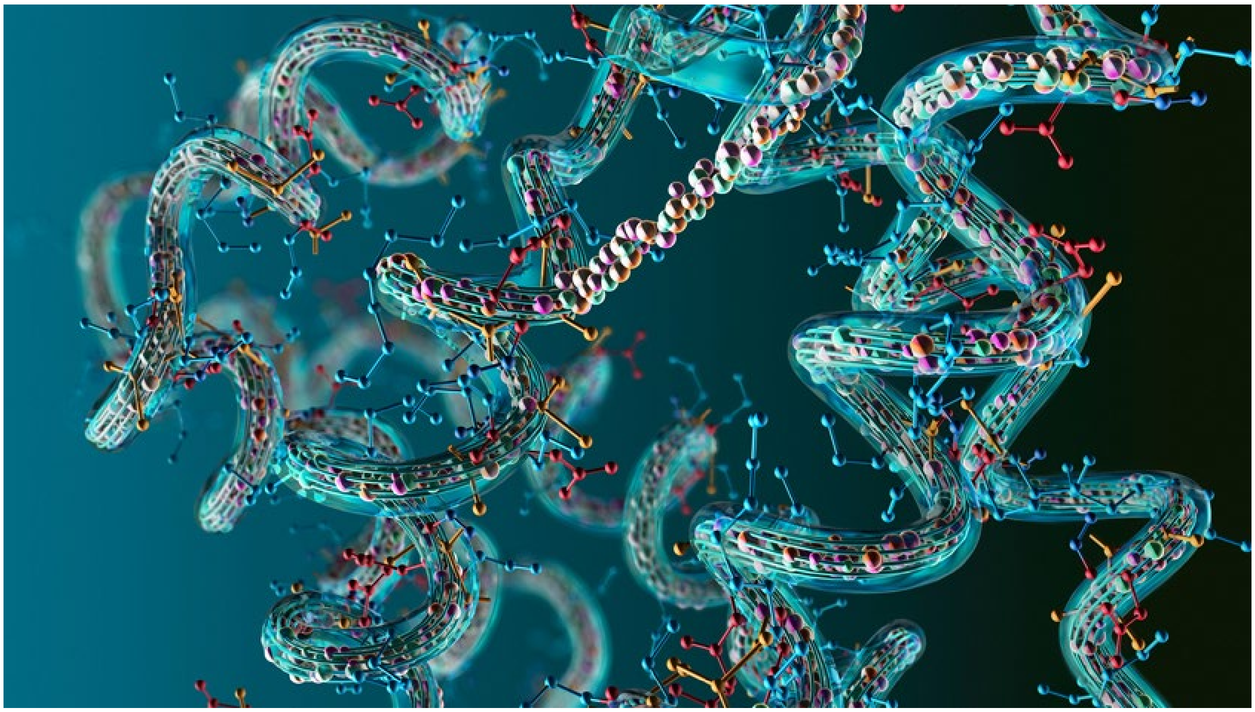
A study led by Dr. Gabor Kovacs at the Krembil Brain Institute revealed new insights into the mechanism underlying Lewy body disorders. These disorders encompass Parkinson disease and dementia with Lewy bodies—two of the most prevalent neurodegenerative diseases.

“Lewy body disorders can lead to a wide range of symptoms, including movement problems, cognitive decline and psychiatric conditions. However, the reason for this symptom variability is unclear. New findings from our lab suggest that the alpha-synuclein protein holds the key to understanding these disorders,” says Dr. Ivan Martinez-Valbuena, the first author of the study and a postdoctoral researcher in Dr. Kovacs’ laboratory.

Alpha-synuclein (αSyn) is a protein that is present in the healthy brain, where it plays a role in the release of neurotransmitters. In Lewy body disorders, αSyn becomes misfolded and clumps together to form aggregates that interfere with normal brain function and lead to the death of nerve cells.

“Previous work has shown that the amounts of misfolded αSyn deposited in the brain cannot fully explain clinical features. Here, we explored whether different forms of the protein may contribute to the symptoms that we see in the clinic,” adds Dr. Martinez-Valbuena.

The researchers used detailed neuropathological and biochemical examinations and protein profiling to explore the characteristics of αSyn in different patients with Lewy body disorders and in different brain regions.



Proteins are made of strands of amino acids (illustrated above) that fold into intricate three-dimensional shapes. When certain proteins fold incorrectly, they can cause diseases such as Lewy body disorders and Creutzfeldt-Jakob disease.

“αSyn can misfold in different ways, and the protein’s shape determines its seeding ability—how easily it can convert nearby ‘healthy’ proteins to misfold and spread throughout the brain,” says Dr. Kovacs, the senior author of the study and a Senior Scientist at the Krembil Brain Institute. “In a general sense, we explored whether we can link clinical features of Lewy body disorders to the type of misfolded αSyn.”

The researchers used a highly sensitive assay called real-time quaking-induced conversion (RT-QuIC) to measure the seeding ability of different types of αSyn. They characterized αSyn in post-mortem tissues from eight brain regions originating from 30 individuals with Lewy body disorders.

The team found a connection between the brain regions with the most aggressive forms of αSyn—those with the greatest seeding ability—and the symptoms experienced by patients. For example, patients with aggressive species of αSyn in the hippocampus—a region involved in learning and memory—had mainly cognitive symptoms. Conversely, when aggressive forms of αSyn were found in the substantia nigra—a region that helps control movements—motor symptoms were more common.

The team also found that the αSyn seeding ability was linked to the speed at which the disease progressed. For example, individuals with the most aggressive forms of αSyn in the substantia nigra had rapid onset disease and developed advanced symptoms in less than three years from diagnosis.

"Our findings suggest that new therapeutic strategies should consider a variety of differently folded αSyn species, rather than a single species," concludes Dr. Kovacs, who is also a Professor in the Department of Laboratory Medicine and Pathobiology and a Principal Investigator at the Tanz Centre for Research in Neurodegenerative Diseases at the University of Toronto.

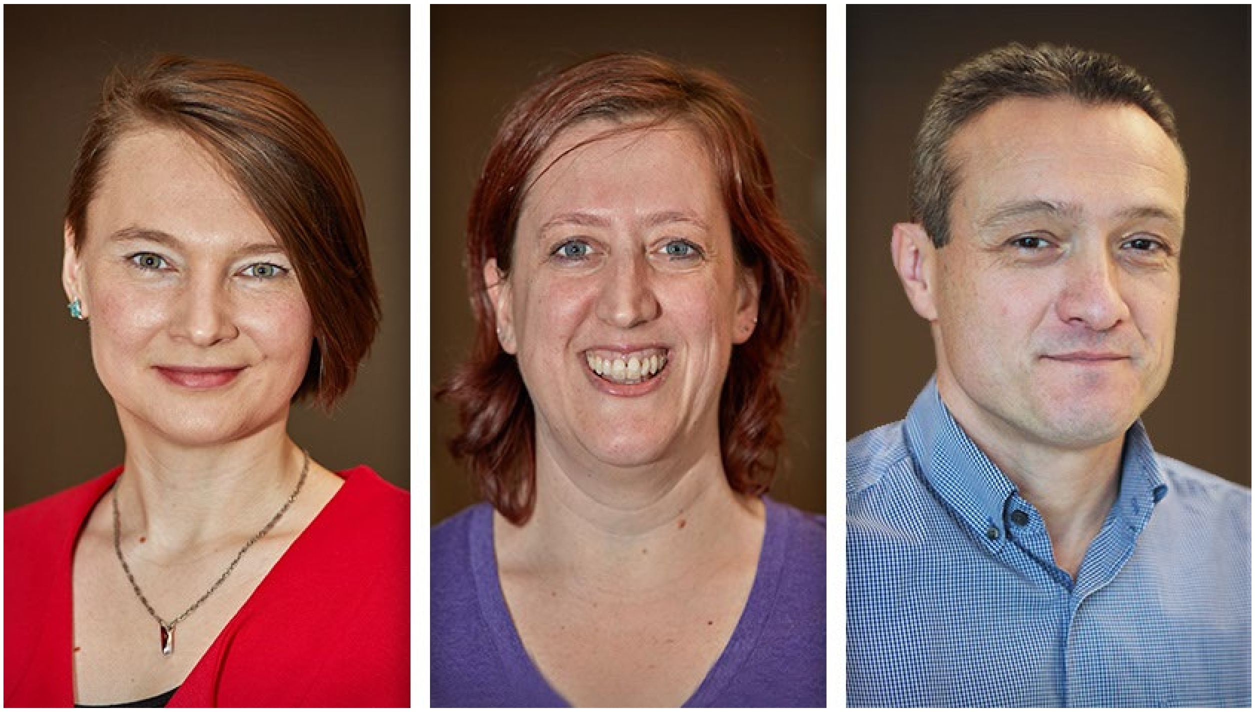
"Targeting the more aggressive types of αSyn that are present in individuals' brains could lead to more effective and tailored treatments."

This work was supported by the Edmond J. Safra Philanthropic Foundation, the Krembil Foundation, the Rossy Foundation, the Maybank Foundation, the Blidner Family Foundation, the Canada Foundation for Innovation, the Ontario Research Fund, the Spanish Ministry of Science Innovation and Universities, and the UHN Foundation. The authors would also like to thank the patients and their families for donating the tissue samples used in this study—this work would not have been possible without their contributions.

Martinez-Valbuena I, Swinkin E, Santamaria E, Fernandez-Irigoyen J, Sackmann V, Kim A, Li J, Gonzalez-Latapi P, Kuhlman G, Bhowmick SS, Visanji NP, Lang AE, Kovacs GG. α-Synuclein molecular behavior and nigral proteomic profiling distinguish subtypes of Lewy body disorders. Acta Neuropathol. 2022 Aug;144(2):167-185. doi: 10.1007/s00401-022-02453-0.

Boost for MicroRNA Research

Researchers enhance online database to support discovery of biomarkers and therapeutic targets.



(L-R) Drs. Anne-Christin Hauschild, Chiara Pastrello and Igor Jurisica.

Investigators at the Schroeder Arthritis Institute have expanded the functionality of an online database that supports microRNA research.

MicroRNAs are short, non-coding RNA molecules that regulate gene expression and cell function at the transcript or protein level. These molecules regulate various biological processes and are involved in the development of a wide range of diseases, including arthritis, brain disorders and cancer.

Dr. Igor Jurisica, a Senior Scientist at the Schroeder Arthritis Institute, maintains a database called the microRNA Data Integration Portal (mirDIP), which his group built more than ten years ago to support microRNA research. His team recently released an updated version of the portal, mirDIP 5.2.

“With their crucial role in disease pathology, microRNAs are good candidates for diagnostic biomarkers or therapeutic targets,” says Dr. Anne-Christin Hauschild, a former postdoctoral researcher in Dr. Jurisica’s research group and co-lead author of the article describing the updated portal. “However, comprehensive information about how microRNAs behave and interact with other molecules in specific environments is lacking, and such details are important for developing targeted therapies.”

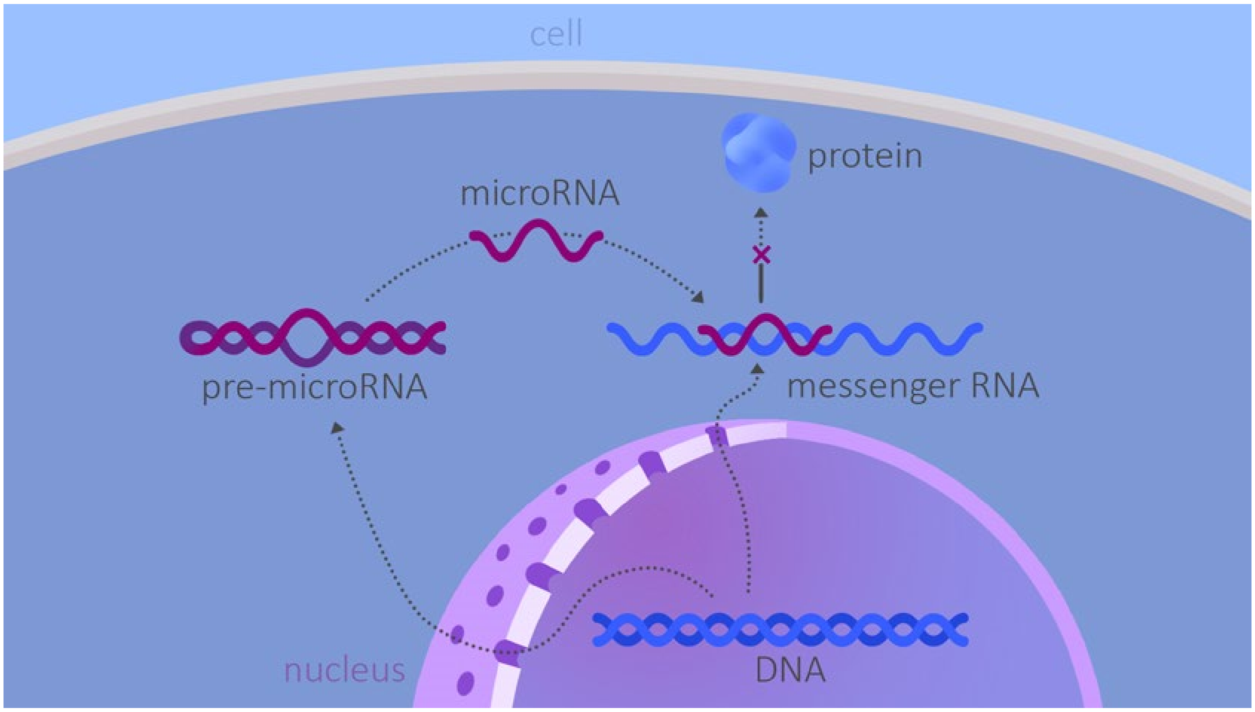
“MirDIP enables researchers to easily identify microRNAs that are relevant to particular genes, pathways and diseases of interest, giving them a starting point for determining the role of these molecules in disease initiation and progression and how they can be targeted with drugs,” adds Dr. Chiara Pastrello, a Scientific Associate in Dr. Jurisica’s research group and co-lead author of the article.

The portal contains a collection of microRNA-related data from multiple databases and prediction algorithms. The team expanded the portal using recent data for 27,576 genes in humans and 32,497 novel microRNAs, and they mapped known and novel microRNAs that target each gene. To help users analyze microRNAs related to a specific tissue or disease, the team also added information for 330 tissue and disease contexts and 123,651,910 gene–microRNA–tissue interactions.

“The updated version of mirDIP is a more comprehensive resource to study microRNA landscapes with minimal biases and more context-specific information about microRNAs and their interactions,” says Dr. Jurisica. “This portal enables the discovery of molecular signatures of various diseases and therapeutic targets that could improve the way we treat them.”

This work was supported by the Ontario Research Fund, the Natural Sciences and Engineering Research Council of Canada, the Canada Foundation for Innovation and the UHN Foundation. *Dr. Anne-Christin Hauschild, a former postdoctoral researcher in Dr. Jurisica’s lab, is a Junior Professor for Medical Informatics at the University of Göttingen. Dr. Chiara Pastrello is a Scientific Associate in Dr. Jurisica’s lab. Dr. Igor Jurisica is a Professor of Computer Science and Medical Biophysics at the University of Toronto.*

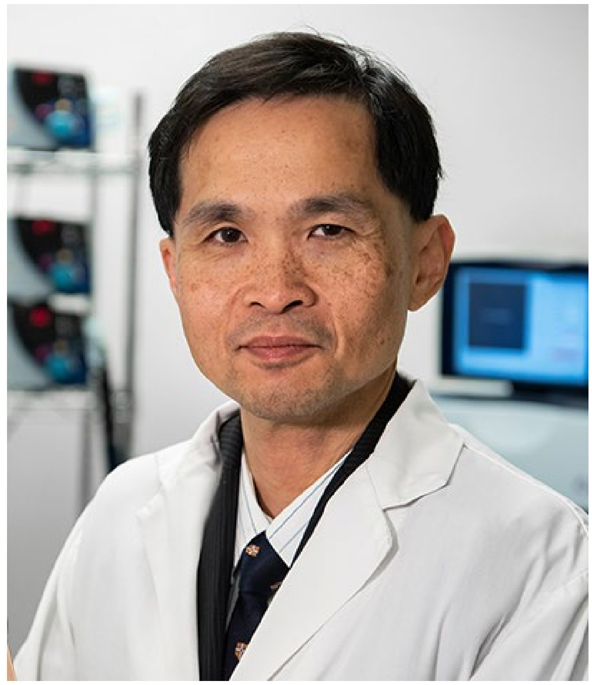
Hauschild AC#, Pastrello C#, Ekaputeri GKA, Bethune-Waddell D, Abovsky M, Ahmed Z, Kotlyar M, Lu R, Jurisica I. MirDIP 5.2: tissue context annotation and novel microRNA curation. Nucleic Acids Res. 2023 Jan 6. doi: 10.1093/nar/gkac1070.
 # indicates joint first authors



Our genetic code, which is held in the nucleus as DNA, is used as a template to make messenger RNA. These RNA molecules serve as 'working copies' of our genes and are used to make proteins. MicroRNAs, which are smaller, non-coding fragments of RNA, can bind to messenger RNA and interfere with this process.

Decoding Neural Signals

Study shows that Parkinson disease treatments affect two types of brain activity differently.



(L-R) Drs. Ghazaleh Darmani and Robert Chen.

Researchers from the Krembil Brain Institute have shed light on the long-term effects of deep brain stimulation on neuronal activity in a brain region involved in Parkinson disease.

A hallmark feature of Parkinson disease is an increase in a type of neuronal activity—known as beta oscillations—in the basal ganglia region of the brain. Previous studies suggest that deep brain stimulation applied to this region reduces motor symptoms of the disease by disrupting this form of patterned neuronal activity.

According to Krembil Senior Scientist Dr. Robert Chen, however, beta oscillations are only one piece of the puzzle.

“When measuring the activity of large groups of neurons, the signals that we acquire are made up of oscillations, or patterned activity, as well as non–patterned, or aperiodic, activity, which is often viewed as background activity,” says Dr. Chen. “To understand precisely how deep brain stimulation treats disease symptoms, we need to consider its long-term effects on patterned and non-patterned forms of neuronal activity.”

To determine the long-term effects of deep brain stimulation in the basal ganglia, Dr. Chen’s team recorded local neuronal activity in patients with Parkinson disease during six study visits over 18 months. They then applied computational methods to separate the oscillatory and aperiodic components of the signals.

“It has previously been very challenging to study the long-term effects of deep brain stimulation on brain activity because we were limited to recording from neurons over a short period while surgically implanting the electrodes,” explains Dr. Ghazaleh Darmani, a postdoctoral researcher in Dr. Chen’s lab and the first author of the study. “In this study, we were able to assess neural signals over a longer period because our patients had specialized devices that can record local activity throughout the study period.”

The team discovered that deep brain stimulation increased aperiodic beta activity over time. In contrast, beta oscillations were stable over time.

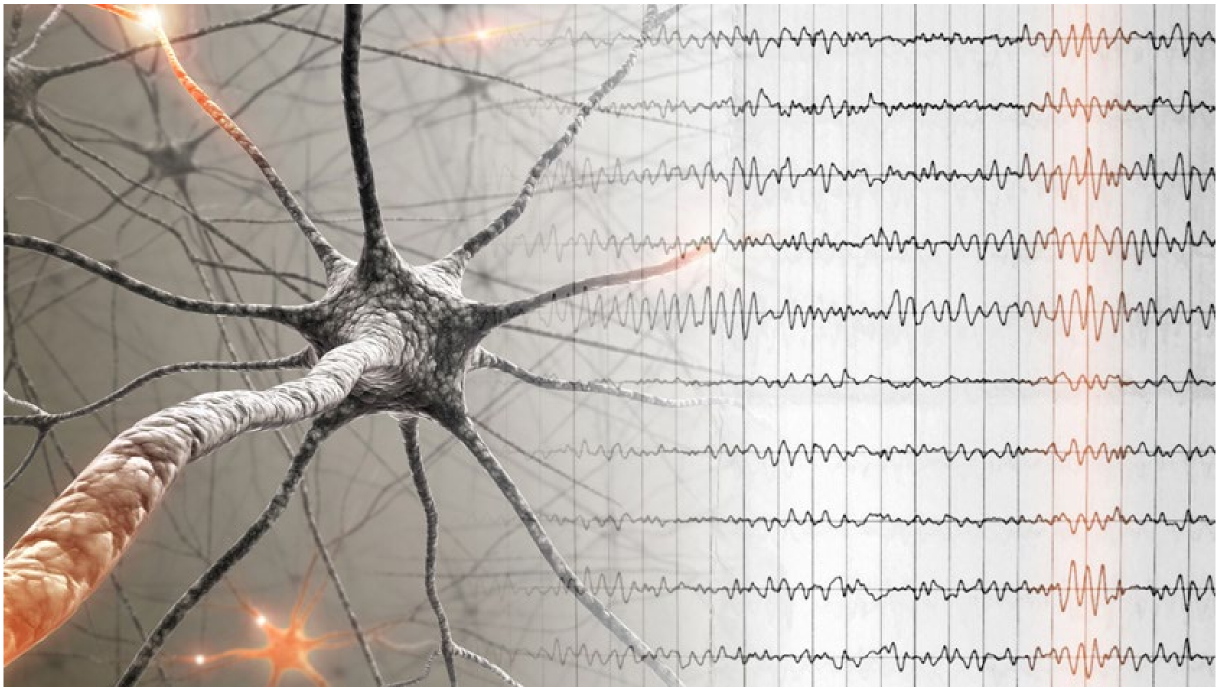
These findings call into question the traditional view that deep brain stimulation treats Parkinson symptoms by reducing beta oscillations in the basal ganglia, and highlight the need to consider different forms of neuronal activity when studying the disease and developing therapies.

The researchers also found that dopaminergic medications that are commonly used to treat the disease affect these two types of brain activity differently. These medications did not affect aperiodic beta activity but did suppress beta oscillations.

“Our findings suggest that beta oscillations and aperiodic activity represent distinct but complementary neural processes in Parkinson disease,” says Dr. Darmani. “Clarifying how each type of activity contributes to disease symptoms is an important step towards developing more targeted and effective deep brain stimulation treatments.”

This work was supported by the Canadian Institutes of Health Research, Medtronic Inc. and the UHN Foundation. Dr. Robert Chen is a Professor in the Division of Neurology, Department of Medicine at the University of Toronto.

Darmani G, Drummond NM, Ramezanpour H, Saha U, Hoque T, Udupa K, Sarica C, Zeng K, Cortez Grippe T, Nankoo JF, Bergmann TO, Hodaie M, Kalia SK, Lozano AM, Hutchison WD, Fasano A, Chen R. Long-Term Recording of Subthalamic Aperiodic Activities and Beta Bursts in Parkinson's Disease. Mov Disord. 2023 Feb. doi: 10.1002/mds.29276.



Neuronal firing can generate either patterned oscillations or non-oscillatory ‘aperiodic’ activity, both of which are seen in electroencephalograms and deep-brain recordings. In the above illustration, oscillatory activity is highlighted in orange on the right.