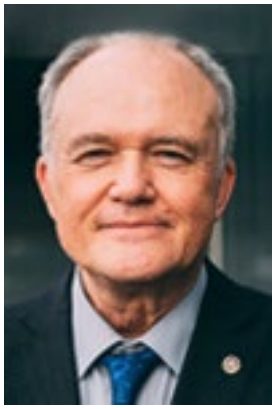
The Krembil

July 2022



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 the exciting news and innovative research happening at the Krembil Research Institute.

Stories in this month's issue:

Donald Weaver, PhD, MD, FRCPC, FCAHS
Director, Krembil Research Institute
University Health Network

News

Krembil Research Day 2022

Trainees and research staff share discoveries in neuroscience, vision and arthritis research.

This year's hybrid Krembil Research Day was attended by more than 220 people and featured 62 oral and poster presentations from Krembil trainees and staff.

Each summer, Krembil Research Day is an opportunity for Krembil trainees, investigators and research staff to come together to celebrate achievements across the Institute's three research pillars: brain and spine, vision, and bone and joints.

This year's Research Day was a two-day hybrid event that enabled members of the Krembil community to connect and discuss research in person and virtually. Day one of the event was hosted online and at the BMO Education & Conference Centre at the Krembil Discovery Tower, and day two was hosted entirely on the GatherTown virtual event space.

The event began with opening remarks from Dr. Mary Pat McAndrews, Chair of the Trainee Affairs Committee and Dr. Brad Wouters, Executive Vice President, Science and Research at UHN. "We're here today to celebrate you, the next generation of

scientists and explorers at Krembil. And we couldn't be prouder that you've chosen UHN as the place where you'll begin your exciting careers," said Dr. Wouters.

Following these remarks, attendees heard an inspiring message to trainees from Krembil Director Dr. Donald Weaver.

Attendees then tuned in to six informative oral presentations from trainees across the Institute's research pillars. They also enjoyed a keynote presentation from Dr. Donna Rose Addis, Senior Scientist at Baycrest's Rotman Research Institute, titled "The imaginative brain: Exploring the personal past and future."

Day 2 of the event continued with 56 poster presentations from trainees and research staff hosted on GatherTown. Attendees were able to explore the virtual conference centre, view the posters, and engage with presenters and colleagues.

The Krembil community thanks the many individuals who made this year's Research Day a resounding success, including Krembil's Trainee Affairs Committee, Administration Team and Public Affairs team, and UHN's Education Technology & Media Services (ETMS), who co-produced day one of the event. We also thank the 40 volunteers who served as presentation judges and the Nadler Family for their generous donation for prizes awarded to presentation winners.

PRESENTATION AWARDS

The following trainees are recipients of awards for best oral and poster presentations:

Oral Presentation Graduate Student Category:

- 1st Prize: John MacMillan (Weaver Lab)
- 2nd Prize: Jenny Zhang (Sivak Lab)

Oral Presentation Postdoctoral Category:

- 1st Prize: Ivan Martinez-Valbuena (Kovacs Lab)

Poster Presentation Graduate Student Category:

- 1st Prize: Akshay Gurdita (Wallace Lab)
- 2nd Prize: Lizbeth Ayoub (McAndrews Lab)
- 3rd Prize: Lauren Banh (Viswanathan Lab)

Poster Presentation Postdoctoral Category:

- 1st Prize: Michelle Barraclough (Touma Lab)
- 2nd Prize: Tarun Arora (Chen Lab)
- 3rd Prize: Michael Tang (Inman Lab)

Congratulations to the winners and everyone who presented their work!

Clinician Researcher Joins Krembil

Dr. Christopher Kim is a surgeon and scientist developing treatments for osteoarthritis.

Dr. Christopher Kim is an Orthopaedic Surgeon and a Scientist at the Schroeder Arthritis Institute.

The Krembil Research Institute is pleased to welcome Dr. Christopher Kim as its newest Scientist. Dr. Kim is an Orthopaedic Surgeon in the Sprott Department of Surgery at UHN, and an Assistant Professor in the Department of Surgery at the University of Toronto.

Prior to joining Krembil, Dr. Kim studied stem cells, gene editing and cell therapeutics in the Institute of Medical Sciences at the University of Toronto, under the supervision of Dr. Andras Nagy at the Lunenfeld-Tasnenbaum Research Institute. His PhD research involves the use of genetically engineered cells to deliver compounds that reduce joint inflammation and cartilage loss in experimental models of osteoarthritis.

“Current therapies for osteoarthritis include anti-inflammatory drugs, physical therapy and injections. These therapies can be very effective at reducing symptoms such as pain and inflammation, but they are not cures,” explains Dr. Kim. “Designer cell therapies that reduce inflammation and repair joint tissues are a new type of treatment with enormous potential for stopping disease progression and helping patients reduce joint pain and inflammation and regain function.”

At Krembil, Dr. Kim will continue this line of research, focusing on gene and cell therapies to treat and prevent osteoarthritis. His surgical practice at the Toronto Western Hospital will focus on hip and knee arthroplasty.

“I admire the supportive, academically rigorous and patient-centered environment here at Krembil,” says Dr. Kim. “I am excited to establish productive collaborations with other scientists and clinicians that expand and enrich our respective research programs.”

Dr. Kim completed his MD at the University of Ottawa and Orthopaedic Surgery residency at the University of Toronto. Following residency, he completed a fellowship in lower extremity reconstruction at the Toronto Western Hospital.

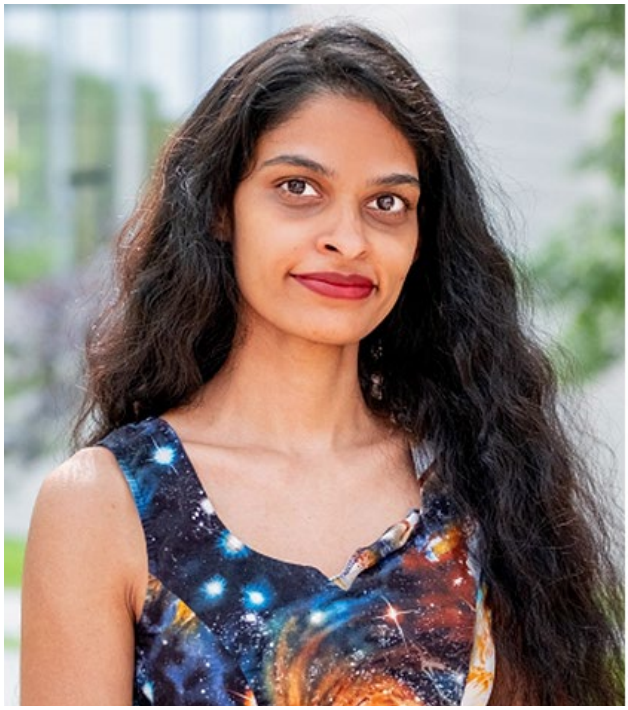
Welcome to Krembil, Dr. Kim!

Dr. Kim’s recruitment was made possible by the generous support of the Toronto Western Hospital Division of Orthopaedic Surgery and the Schroeder Arthritis Institute.

Research

Improving Concussion Policies

Researchers develop the first expert consensus on concussion policies for the school setting.



(L-R) Swapna Mylabathula, MD/PhD student in Dr. Tator's lab and first author of the study (Photo: Changmo Joseph Kim), and Dr. Charles Tator, Emeritus Scientist at the Krembil Brain Institute and senior author of the study.

Researchers at the Krembil Brain Institute, the Hospital for Sick Children and the University of Toronto have developed a comprehensive list of recommendations for concussion policies for the school setting.

Concussions are a significant public health issue and several government-initiated policies address concussion diagnosis, management and prevention, particularly in student athletes in elementary and secondary schools.

According to Dr. Charles Tator, an Emeritus Scientist at the Krembil Brain Institute and Director of the Canadian Concussion Centre, "school-based concussion policies vary widely in content and in the way that they are implemented."

Dr. Tator explains that increasing consistency between policies is an important first step towards ensuring that they are applied effectively and have a positive impact. “If we can streamline policies, we can reduce confusion and facilitate communication among various stakeholders, including educators, students, parents and guardians, and clinicians. We can also better allocate funding to support policy development and implementation.”

Dr. Tator’s team comprised Swapna Mylabathula, an MD/PhD student in Dr. Tator’s lab and first author of the study, Dr. Colin Macarthur, a Senior Scientist at the Hospital for Sick Children, and Drs. Astrid Guttmann and Angela Colantonio, Professors at the University of Toronto. The team brought together 20 experts who have roles in concussion prevention and management to form the Concussion Policy Consensus Group—tasked with reviewing school-based policies and developing recommendations to improve their consistency. This group included public health representatives, policymakers, clinicians, school board representatives, and parents and guardians of students who have experienced a concussion. The group also included members of Parachute Canada—a national injury prevention organization—and the Ontario Physical and Health Education Association.

After providing feedback about an initial set of recommendations prepared by the research team, the experts met by teleconference to discuss recommendations and suggest revisions. This process was repeated, resulting in a comprehensive list of 30 recommendations that spanned concussion education, prevention and communication, as well as best practices for return-to-learn or play following a concussion.

Final recommendations for concussion policies included:

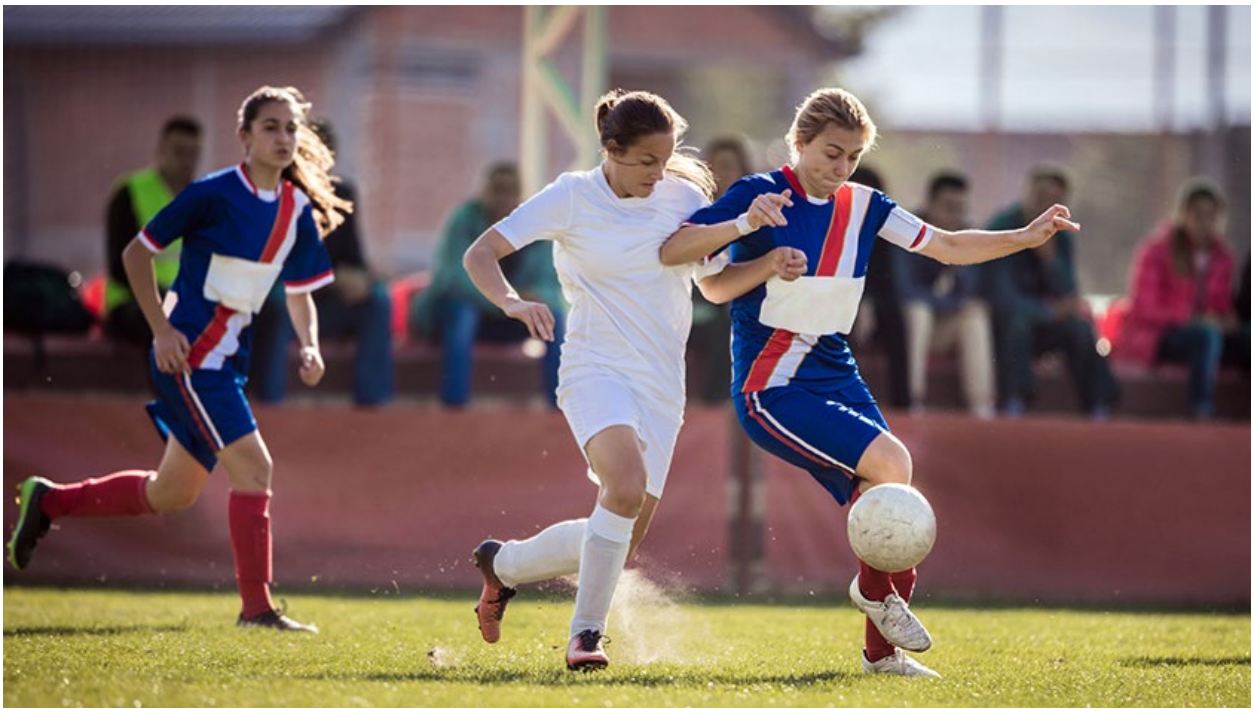
1. Outlining that concussion education should be required for coaches, referees, trainers, teachers, school staff, students, and parents and guardians;
2. Specifying which individuals are responsible for planning return-to-learn or play following a concussion;
3. Outlining that schools should communicate information about previous concussions for students moving between grades or schools; and
4. Requiring that concussion surveillance data be collected at the school level and collated by school boards and the province or territory to help assess the policy’s impact.

This list of recommendations represents the first expert consensus for school-based concussion policies and reflects the diverse perspectives of a multidisciplinary group of stakeholders in and outside the school system.

“The aim of these recommendations is to safeguard the well-being of children and youth by improving concussion management and prevention in the school setting,” says Swapna. “An important next step is to assess the feasibility of implementing these recommendations and the impact of the new policies on concussion in schools.”

This work was supported by the UHN Foundation. Dr. Astrid Guttmann holds a Tier I Canada Research Chair in Applied Child Health Services and Policy at the University of Toronto. Dr. Angela Colantonio holds a Tier I Canada Research Chair in Traumatic Brain Injury in Underserved Populations at the University of Toronto. Dr. Charles Tator is a Professor in the Department of Surgery at the University of Toronto.

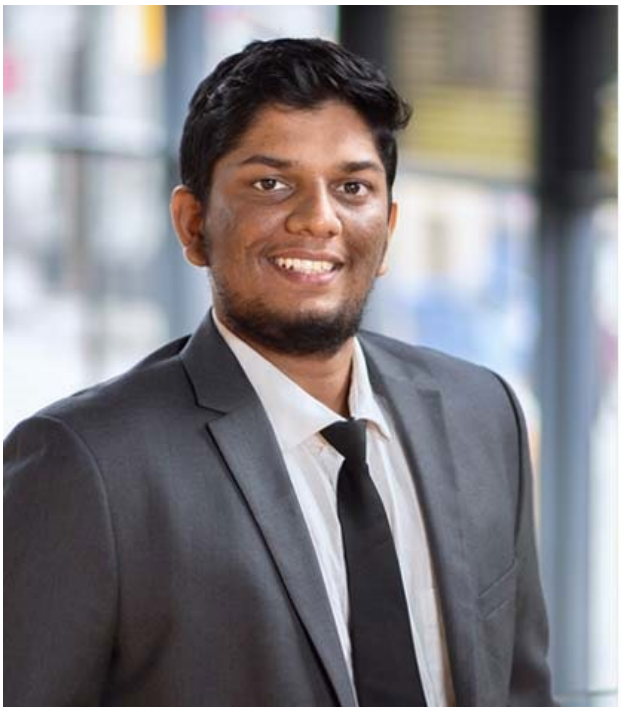
Mylabathula S, Macarthur C, Guttmann A, Colantonio A, Tator C. Development of a concussion public policy on prevention, management and education for schools using expert consensus. Inj Prev. 2022 May 4. doi: 10.1136/injuryprev-2021-044395.



School-aged athletes competing in contact and non-contact sports are at risk for concussions. Sports-related concussions in the school setting have drawn considerable attention from Ontario policymakers.

It Gets Harder with Age

Researchers find that symptoms of a rare form of epilepsy worsen in adults as they age.



(L-R) Arunan Selvarajah, MSc graduate from Dr. Andrade's lab and first author of the study, and Dr. Danielle Andrade, Clinician Investigator at the Krembil Brain Institute, Medical Director of the Epilepsy Program and Director of the Adult Genetic Epilepsy (AGE) Program at UHN.

A recent study from the Krembil Brain Institute provides insights into how a severe form of epilepsy known as Dravet syndrome affects older adults.

Dravet syndrome is a rare, lifelong condition that begins in infancy and causes frequent seizures. Other common symptoms in children with Dravet syndrome include developmental delay and problems with balance and walking. Seizure frequency tends to decrease in adulthood, but other symptoms of Dravet syndrome have not been well-characterized in adults.

To deepen our understanding of how Dravet syndrome affects adults, a team led by Dr. Danielle Andrade, a Clinician Investigator at the Krembil Brain Institute and Medical Director of UHN's Epilepsy Program, examined motor symptoms, such as difficulty walking, resting tremor and abnormal body movements. Participants were recruited through the Adult Genetic Epilepsy (AGE) Program at Toronto Western Hospital.

“Parents of those with Dravet syndrome often report that their children lose certain skills, including the ability to walk, when they become adults,” says Arunan Selvarajah, an MSc graduate from Dr. Andrade’s lab and first author of the study. “We wanted to objectively test these age-related changes to better understand the disease and improve how we manage it.”

The team used standard assessment tools to evaluate two groups of patients: a smaller group of patients was observed over a five-year period between 2014 and 2019, and another larger group of patients was evaluated between 2019 and 2020.

The team found that five of the six individuals with Dravet syndrome in the smaller group experienced a worsening of motor symptoms over the five-year study period. Of note, the two oldest patients in the group were no longer able to walk five years after their first assessment.

Using tests of motor function in the larger group of participants, the researchers found that age was associated with more difficulty in rising from a chair and walking, as well as slower movement. In addition, patients with Dravet syndrome had more trouble walking than older individuals without the condition.

“To our knowledge, this is the first study to follow a group of adult patients with Dravet syndrome,” says Dr. Andrade. “We found that symptoms related to mobility worsen with age. Next steps for this research include determining why this happens and if it is possible to slow or prevent it.”

This work was supported by the Dravet Syndrome Foundation, Dravet Canada and the UHN Foundation. Dr. Danielle Andrade is a Professor of Medicine at the University of Toronto.

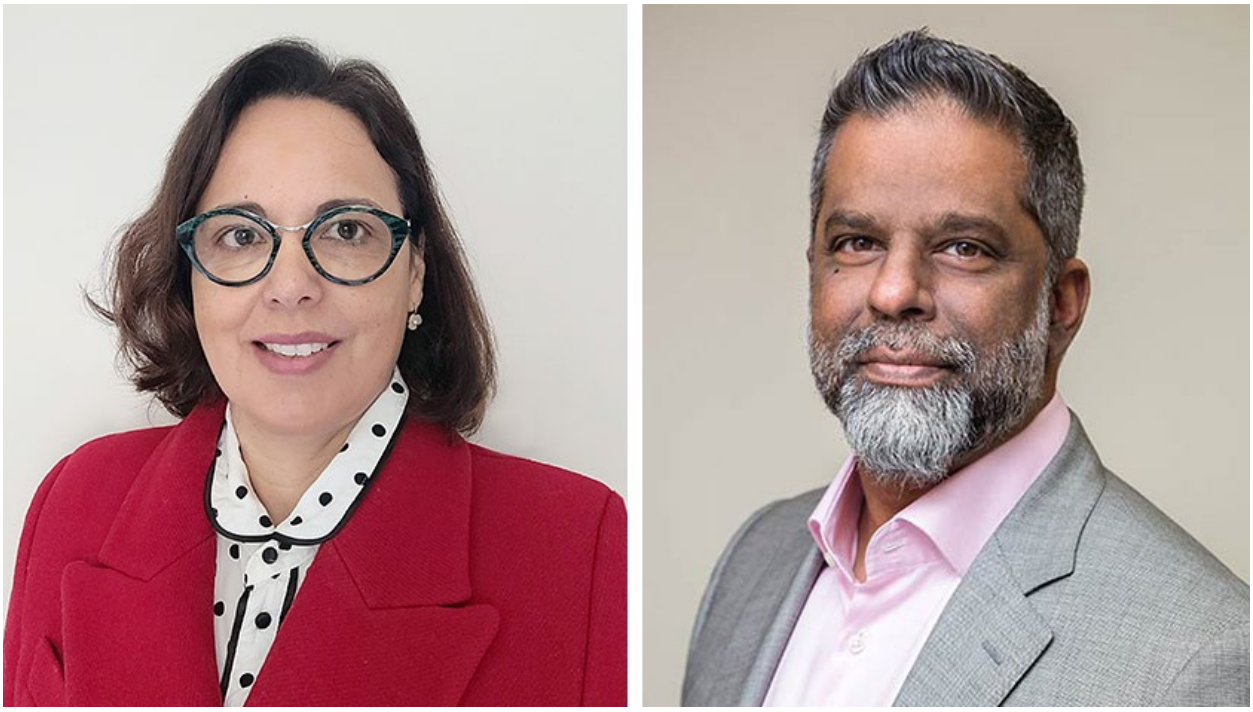
Dr. Andrade serves on the medical advisory boards of the Dravet Syndrome Foundation and Stoke Therapeutics. She is on the speakers bureau for Eisai and Biocodex, and has participated in investigator-initiated research for Biocodex and Dravet Syndrome Foundation. Dr. Berg is on the speakers bureau for Biomarin and sits on the advisory board for Zogenix and Neurocrin.

Selvarajah A, Gorodetsky C, Marques P, Zulfiqar Ali Q, Berg AT, Fasano A, Andrade DM. Progressive Worsening of Gait and Motor Abnormalities in Older Adults with Dravet Syndrome. Neurology. 2022 May 31. doi: 10.1212/WNL.0000000000200341.

Symptoms of Dravet syndrome begin in the first year of life. As affected individuals reach adulthood, caregivers often report worsening motor symptoms, such as a reduced ability to walk.

What Do You Expect?

Study shows fulfilling patients' pre-surgery expectations is key to increasing satisfaction.



(L-R) Drs. Mayilee Canizares and Raja Rampersaud.

A new study led by researchers at the Schroeder Arthritis Institute has shed light on factors contributing to patient satisfaction following spine surgery.

Doctors often look to patient satisfaction to gauge the success of orthopaedic and other procedures, but satisfaction can be influenced by more than just the results of a procedure.

“Pre-surgery expectations are known to be generally a good predictor of how satisfied a patient will be with elective spine surgery, but expectations are often related to other factors that influence satisfaction, such as expectation fulfilment and reduced pain and disability following surgery,” explains Dr. Raja Rampersaud, a Clinician Investigator at the Schroeder Arthritis Institute and co-first author of the study.

To determine the best predictors of patient satisfaction, Dr. Rampersaud’s team examined how patients’ satisfaction with spine surgery is influenced by a variety of patient factors.

The researchers examined data from over 1,860 patients who underwent elective surgery for spinal conditions, such as disk herniation and narrowing of the spaces within the spine.

Before surgery, patients were asked what their expectations were for the surgery—for example, whether they expected it to reduce pain or improve mobility and independence. Following surgery, patients reported whether their expectations for the surgery were fulfilled. The research team also measured patients' pain and physical disability before the surgery and one year after the surgery to see if it led to measurable improvements.

Approximately 85% of patients were satisfied with their surgery and over 82% of patients reported that at least one of their expectations was met.

Although individuals with higher pre-surgery expectations were less likely to have their expectations fulfilled, they were more likely to experience reduced pain and disability. One possible explanation for this is that patients with greater expectations have better compliance with pre- and post-surgery treatment regimens, such as rehabilitation, that contribute to outcome improvement.

Fulfilment of pre-surgery expectations was the most influential factor for patient satisfaction. The research team found that if pre-surgery expectations were fulfilled, patients were more satisfied with their surgery, regardless of the measurable outcomes.

"Our findings indicate that we can improve patients' satisfaction with spine surgery by working with them to minimize the discrepancy between their expectations and the most likely surgical outcomes," explains Dr. Mayilee Canizares, a Scientific Associate at the Schroeder Arthritis Institute and co-first author of the study. "We hope that this study informs how clinicians approach pre-surgery consultations, not just for orthopaedic procedures but for all elective surgeries."

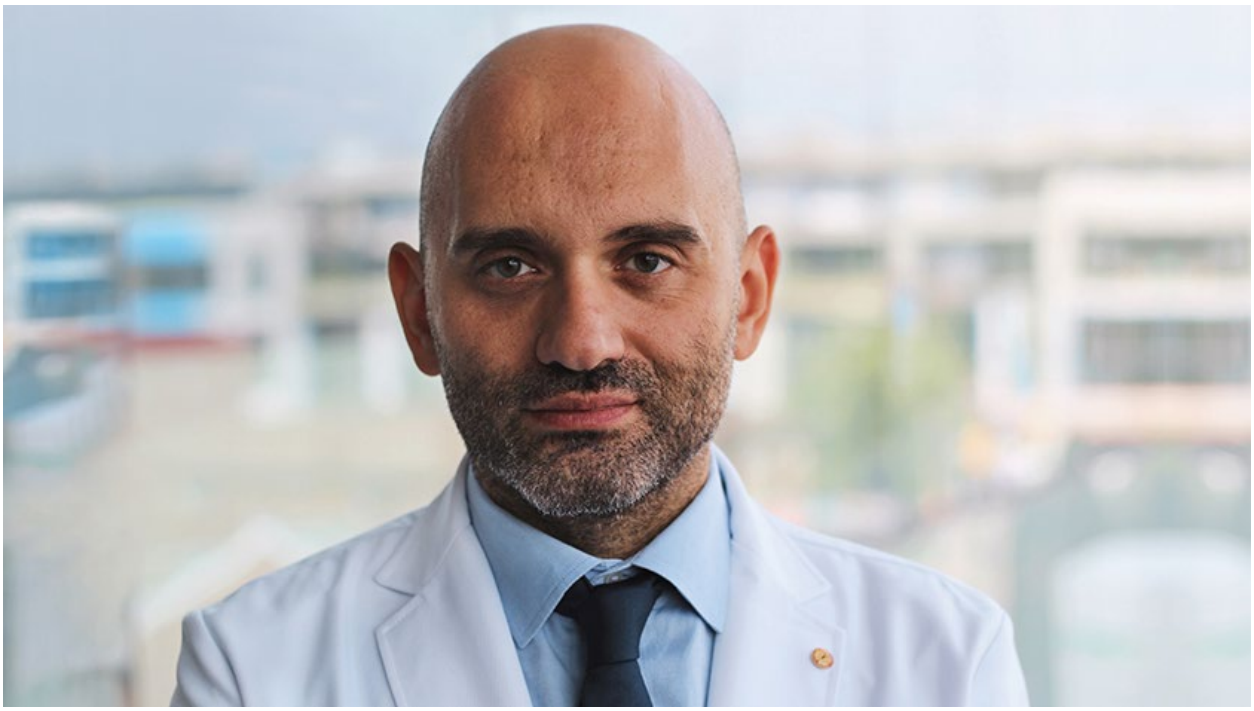
This work was supported by the UHN Foundation. Dr. Raja Rampersaud is a Professor of Surgery at the University of Toronto and a Staff Orthopaedic Surgeon at the Toronto Western Hospital.

Rampersaud YR, Canizares M, Perruccio AV, Abraham E, Bailey CS, Christie SD, Evaniew N, Finkelstein JA, Glennie RA, Johnson MG, Nataraj A, Paquet J, Phan P, Weber MH, Thomas K, Manson N, Hall H, Fisher CG. Fulfillment of Patient Expectations After Spine Surgery is Critical to Patient Satisfaction: A Cohort Study of Spine Surgery Patients. Neurosurgery. 2022 Apr 22. doi: 10.1227/neu.0000000000001981.

Clinicians can improve patients' satisfaction with spine surgery by assessing pre-surgery expectations and ensuring that they align with likely surgical outcomes.

Smart Treatments on Horizon

Researchers develop an approach to better tailor deep brain stimulation to patients' needs.



Dr. Alfonso Fasano at the Krembil Discovery Tower, located at the Toronto Western Hospital.

Researchers at the Krembil Brain Institute have developed a strategy to use patients' brain activity to guide the programming of deep brain stimulation (DBS).

Many symptoms of neurological disorders, from tremors in Parkinson disease to seizures in epilepsy, are caused by neurons misfiring. DBS is a promising treatment for these disorders that uses electrodes implanted in the brain to send electrical impulses to change neuron firing patterns.

"There is no simple correct or incorrect way for neurons to fire; different firing rates and patterns underlie different behaviours depending on the brain regions involved," explains Dr. Alfonso Fasano, a Krembil Clinician-Investigator, scientist at CRANIA and first author of the study. "Even with a successful surgery to implant DBS electrodes, it can be a difficult process of trial and error to find a stimulation pattern that improves a patient's symptoms."

In some conditions, such as Parkinson disease, symptoms can improve within minutes of applying an effective stimulation pattern. For others, such as epilepsy or the

movement disorder dystonia, optimizing DBS treatment can be more difficult because it can take days or weeks to see if there has been an improvement.

Using a recent breakthrough in DBS technology that enables chronic recordings of brain activity, researchers led by Dr. Fasano developed a DBS programming strategy and tested it in two individuals—one with epilepsy and one with dystonia.

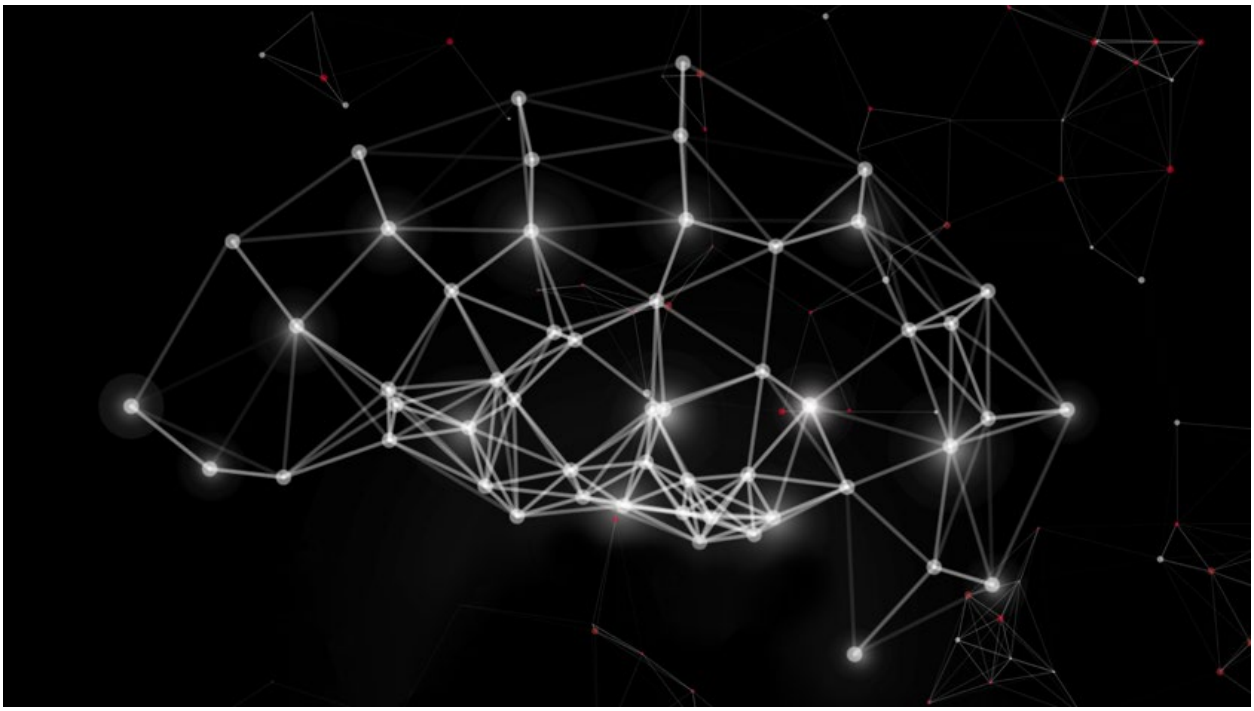
The team, which included researchers from Krembil, the KITE Research Institute and the Hospital for Sick Children, used implanted electrodes to record brain activity whenever a patient indicated that they were experiencing a particular symptom.

Using this information, the researchers identified unique patterns of neuron activity while symptoms were occurring in localized brain areas. Next, they programmed a series of electrical pulses targeted at these brain areas, which helped to reduce symptoms. For the individual with epilepsy, this approach reduced the number of seizures by over 90% over the two-week observation period, an outcome usually achieved over months of attempts. Similarly, within a few days, the individual with dystonia experienced sufficient symptom improvement to leave the ICU, where they were being treated for a life-threatening acute worsening of their condition.

“This approach is potentially game-changing. In addition to helping us tailor DBS to individual patients, this approach could eventually be used to create smart DBS that can respond to a patient’s changing symptoms in real-time,” concludes Dr. Fasano. “Our next steps will be to test this approach in more patients and compare its effectiveness with that of traditional approaches.”

This work was supported by the University of Toronto (UofT) and the UHN Foundation. CRANIA was established with support from the Canada Foundation for Innovation. Dr. Alfonso Fasano is scientist at CRANIA, a Professor at UofT and the Chair in Neuromodulation at UofT and UHN.

Fasano A, Gorodetsky C, Paul D, Germann J, Loh A, Yan H, Carlen PL, Breitbart S, Lozano AM, Ibrahim GM, Kalia SK. Local Field Potential-Based Programming: A Proof-of-Concept Pilot Study. Neuromodulation. 2022 Feb. doi: 10.1111/ner.13520.



CRANIA is a world-class center for the research and development of neuromodulation technologies and interventions in Toronto. To learn more about how Dr. Fasano and other CRANIA scientists are advancing DBS, visit CRANIA.ca.