KREMBIL

Krembil Brain Institute

ALZHEIMER'S RESEARCHERS ARE GETTING CLOSER TO A BREAKTHROUGH

CRACKING CHRONIC PAIN'S SECRET CODE

FINDING ACCEPTANCE IN EPILEPSY

UNLOCKING THE BRAIN'S BIGGEST MYSTERIES

How scientists are using artificial intelligence to find new drugs for Parkinson's

Toronto Western Hospital UHN

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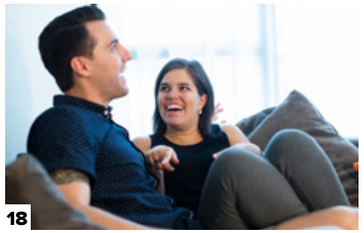

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NO ONE IN CANADA IS DOING MORE FOR BRAIN HEALTH THAN US

Of all the organs in the human body none are more vital to determining who we are than the one located inside your head.

The brain is more complex and sophisticated than the world's most powerful supercomputers. While it only weighs about three pounds, it contains billions of brain cells that generate more than 50,000 thoughts per day.

Our brains are wired, literally, by a complicated network of connections that – if stretched end-to-end – would measure thousands of kilometres.

This web of connectivity is as unique as a fingerprint.

But the brain is also fragile. And it's easy to find evidence of this all around us. Just ask any one of the thousands of Canadians who experience a malfunctioning of basic brain function and health each year.

From dementia and Parkinson's disease, to stroke and epilepsy, the number of diseases, disorders and injuries of the brain, spinal cord and nervous system now exceeds 1,000.

The price tag for neurodegenerative diseases alone is about $60 billion, and as our population ages, these expenses are only expected to grow.

It's for this reason University Health Network (UHN) has established the Krembil Brain Institute at Toronto Western Hospital.

This new institute brings together the doctors, nurses and other clinical care leaders at the world-renowned Krembil Neuroscience Centre with UHN's researchers and neuroscientists at the Krembil Research Institute.

In the pages ahead, you will read about how our teams, working side-by-side, are accelerating research discoveries in areas that improve clinical outcomes and standards of care.

The Krembil Brain Institute is home to the largest and most specialized group of experts in Canada working together to tackle brain-based problems. These experts are pursuing better treatments and cures for diseases of the brain, spine and nerves and seeking to discover innovative tools for early detection and prevention.

Dr. Gelareh Zadeh
Neurosurgeon, Senior Scientist, Program Medical Director, Co-director at the Krembil Brain Institute

Dr. Donald Weaver
Neurologist, Senior Scientist, Research Director, Co-director at the Krembil Brain Institute

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It is estimated that one in three Canadians will be affected by a brain disease, disorder or injury in their lifetime, and that 3.6 million Canadians are currently affected by a neurological condition.

Establishment of the Krembil Brain Institute allows us to position ourselves as the predominant leader in brain health and research today, tomorrow and for years to come – and to develop treatments that can more rapidly go from the bench to the bedside, and ultimately, to humankind.

Sincerely,

Dr. Gelareh Zadeh Dr. Donald Weaver

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KREMBIL BRAIN INSTITUTE

EDITOR
Bryan Borzykowski

ART DIRECTOR
Kamille Chin

PHOTOGRAPHY
Tim Fraser

COVER ART
Tony Lei

CONTRIBUTORS
Sarah Barmak
Claire Gagne
Wendy Glauser
Mark Mann
Diane Peters
Anna Sharratt
Renee Sylvestre-Williams

GLOBE CONTENT STUDIO

MANAGING DIRECTOR
Tracy Day

MANAGING EDITOR
Sean Stanleigh

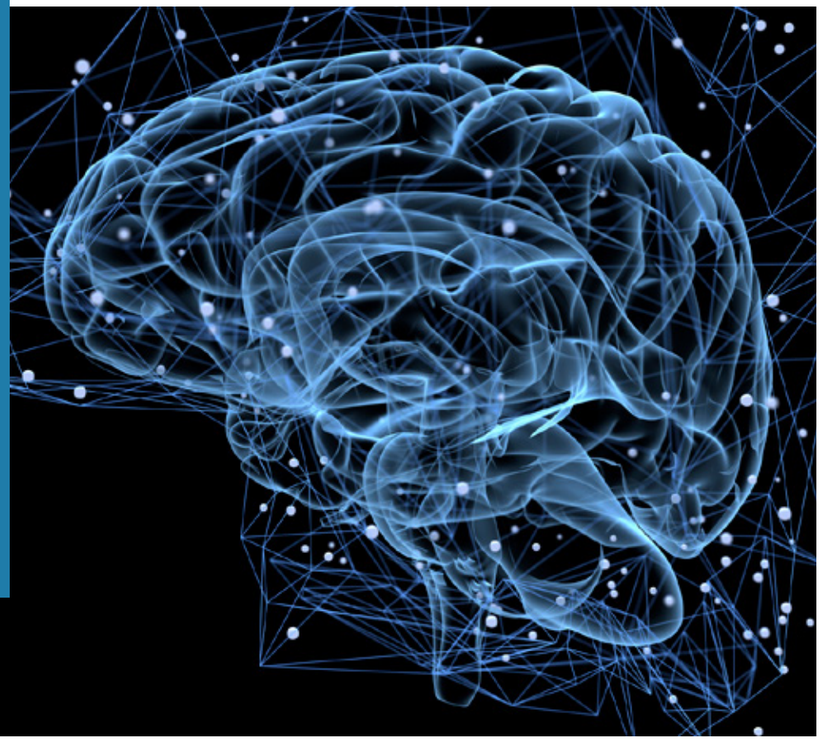
PROGRAM MANAGER
Christina Lippa

PRODUCTION CO-ORDINATOR, THE GLOBE AND MAIL
Isabelle Cabral

BY THE NUMBERS

Krembil Brain Institute

The Krembil Brain Institute is home to the largest and most specialized team of neuro professionals in Canada, and the largest combined clinical and research neurological facilities in North America. Here are some key things you need to know about Krembil and the diseases it researches and treats



INSIDE KREMBIL BRAIN INSTITUTE

100+
Neurosurgeons, neurologists, neuroradiologists, neuroanesthesiologists, neuropsychologists, neurointensivists and neuroscientists at Krembil

400
Nurses and other allied health professionals employed by Krembil

100+
Researchers focused on neuroscience

112,330
Outpatient visits each year

3,340
Inpatient visits each year

2,575
Neurosurgical procedures performed each year

154,000+
Square feet of dedicated research space

BRAIN HEALTH IN CANADA

1 in 3
Canadians affected by a brain disease, disorder or injury in their lifetime (Brain Canada)

50,000
Canadians who experience a stroke each year
(Heart and Stroke Foundation)

1,000+
Number of diseases, disorders and injuries that affect the brain, spinal cord and nervous system
(Brain Canada)

42
Number of Canadians diagnosed with epilepsy every day (Epilepsy Canada)

1 in 5
Adults with chronic pain
(Centers for Disease Control and Prevention)

500,000
Canadians with Alzheimer's disease (Alzheimer Society of Canada)

100,000
Canadians with Parkinson's disease
(Parkinson Canada)

$60 billion
Cost of dementia and neurodegenerative diseases to the Canadian economy each year
(Brain Canada)

How implants can kickstart the brain

At CRANIA – the CenteR for Advancing Neurotechnological Innovation to Application – clinicians, neuroscientists and engineers are combining state-of-the-art technology with the human brain. They are developing implants that can jumpstart parts of the brain that are affected by such diseases as Parkinson's, epilepsy, stroke and Alzheimer's disease. These devices will one day also be able to treat spinal cord and peripheral nerve function. Here's what you need to know about CRANIA

3 to 5 years

The timeline for refining many of these devices, making them more accurate – and available – to Ontarians.

$9 million

Cost of equipment in a soon-to-be developed neuromodulation suite at Krembil. This operating suite will include advanced MRI imaging and special equipment to precisely target regions of the brain.

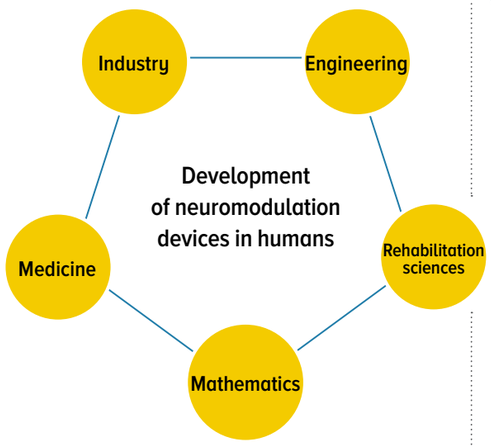
WHO'S LEADING THE RESEARCH?

Directors of CRANIA

Dr. Milos Popovic
Institute Director, Toronto Rehabilitation Institute, University Health Network; Krembil Brain Institute collaborator

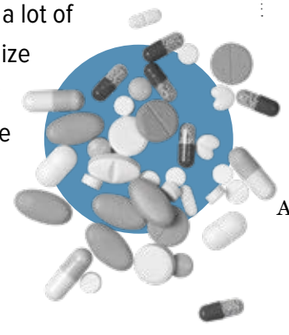
Dr. Taufik Valiante
Co-director, Epilepsy Program, University Health Network; Neurosurgeon and Scientist, Krembil Brain Institute

A TEAM EFFORT



"It's hard to convey the excitement in the field. There are so many things changing so rapidly. With our aging population there are a lot of conditions that will be costing society a lot of money. We realize that we are not going to be able to fix these things alone."

– Dr. Taufik Valiante



2018

747,000 Canadians living with dementia[1]

2031

937,000 Canadians living with dementia

an increase of 66%[2]

18.9%

Percentage of Canadians over age 18 suffering from chronic pain[3]

50%

Percentage of Canadians who will have or have had a mental illness by age 40[4]

CONDITIONS THAT COULD BE TREATED

Parkinson's
Epilepsy
Stroke
Spinal cord injury
Alzheimer's and dementia
Depression
Chronic pain

Sources: [1]Alzheimer Society Canada, 2011 figures. [2]Alzheimer Society Canada, 2018. [3]Pain Research and Management, Nov.-Dec., 2011. [4]Canadian Mental Health Association, 2013.

Q&A

A quicker way to treat depression

Dr. Jonathan Downar discusses how an innovative brain-imaging technology could help patients with mental illness feel better faster

Anna Sharratt

Anyone who has suffered from depression knows it can take years to find a treatment that works. An underused technology, though, could speed up that process and allow doctors to treat this illness in ways they haven't been able to before.

In 2002, Health Canada approved repetitive transcranial magnetic stimulation (rTMS), a treatment technique using a device that delivers powerful magnetic pulses through a coil held close to the head. Pulses activate the brain's neurons and can rewire and reset their connections, which then helps the brain to work properly. This technology has been slow to catch on – it requires lengthy sessions and it's expensive. We spoke to Dr. Jonathan Downar, co-director of University Health Network's rTMS clinic, who says that's changing.

WHY DOES rTMS WORK SO EFFECTIVELY TO TREAT A RANGE OF PSYCHIATRIC DISORDERS?

We have various brain networks that help with basic functions like vision, hearing and movement, or complex functions like regulating thoughts and emotions. One network, called the salience network, is essential for the self-control of thoughts, behaviours and emotions. A course of rTMS to this network can restore its activity. Patients say they feel more in control and have a better capacity to cope with stress without getting overwhelmed.

WHAT'S HAPPENED WITH rTMS LATELY?

A recent brain-stimulation study conducted by three rTMS centres (Krembil, CAMH and UBC) examined the effectiveness of intermittent theta burst stimulation (iTBS), a newer form of rTMS. It found that treatments can be shortened from 38 minutes to three minutes. Thanks to our study, the iTBS treatments were recently approved by the U.S. Food and Drug Administration.

WHAT DOES THAT MEAN FOR PATIENTS?

Clinics can provide access and treatment to many more patients a day. The treatment will also cost less – about $1,000 instead of up to $10,000. This could finally lead to rTMS being covered by most Canadian provinces.

WHERE DO YOU SEE rTMS GOING?

It's expanding. There are more than 1,300 clinics today in the U.S., with hundreds opening in China. There are fewer than 25 clinics in Canada, but we hope this will improve. The techniques are also getting faster and safer. Some studies show that you may be able to get the full effect in as little as five to 10 days by giving multiple sessions per day.

Surgical training goes the distance with new web tool

Krembil's NEURONproject is training the next generation of neurosurgeons around the globe

Anna Sharratt

Health resources are scarce in low- and middle-income countries. With many patients and relatively few doctors, it can be difficult to give surgeons in these areas the best possible training. Many surgical programs need greater structure to their curriculum, including more insights around when to operate and what research studies can help improve care.

This need drove the creation of the non-profit NEURONproject (Neurosurgical Education with Universal Reach ONline), a web-based education hub that offers neurosurgery residents long-distance surgical training. Established in 2011 and funded through private donations, the project helps surgeons learn how to make sound decisions and manage patients in the most ideal manner. Surgeons can access information and connect with faculty remotely from anywhere in the world.

"We frequently think of surgery as mainly technical skills," says Dr. Mojgan Hodaie, founder of NEURONproject, and a Krembil Brain Institute neurosurgeon. "But there is a wealth of knowledge and a clear structure of decision-making that allows us to apply the technical skills at the right time, for the right patient. It is the combination of these two different skill sets that characterizes surgical competency."

To that end, NEURONproject uses an online curriculum to achieve two clear objectives: Ensuring doctors have a strong knowledge base in the clinical sciences and helping them focus on the management of specific diseases and cases. It's currently partnered with sites in Southeast Asia, such as the emerging training program in Cambodia, says Dr. Hodaie.

"We're delivering the foundations of the curriculum to residents online," she says. "We interact in an online class environment and meet face-to-face about once a year, when we have several days of workshops and intense case discussions."

This kind of program is especially important in a region like Southeast Asia, where crowded streets and complicated city layouts are a huge source of head and spine traumas. Improving neurosurgery will have a big impact, says Dr. Hodaie. "This program is an important humanitarian endeavour," she says. "Better training assists them in helping their people and their communities."

The search for an Alzheimer's cure

A curative treatment has proven elusive, while big pharma has abandoned the cause. Researchers at Krembil, though, are getting closer to a breakthrough

Sarah Barmak

Alzheimer's patient Cairine Scott and her husband, Henderson, steal a moment outside Belmont House, a Toronto-based retirement home.

At age 80, Cairine Scott has a glow that most people would envy. Her eyes twinkle beneath a sweep of fine silver hair, and she chuckles at the old stories her 86-year-old husband, Henderson, brings up about the rich lives they've led together. During an afternoon lunch in June, Cairine looks flawless in a textured red-and-green jacket. She's also wearing elegant green-gold earrings and sporting a fiery-red manicure, all of which go well with her hobby of painting brightly coloured canvases, many of which decorate their room.

Cairine, a former elementary school teacher, has certainly led a full life, but she now has trouble remembering the life she's lived. Cairine has Alzheimer's disease, and although she follows the lunchtime conversation, she may not remember today's meal, nor the visitors who ate with her. After lunch, she shows off the library she designed a decade ago for the residents of Belmont House, one of Toronto's best-appointed retirement homes, where she and her husband, a former university professor, live. A plaque on a shelf recognizes Cairine for her work on the library. Today, it's getting harder for her to read any books, or even spell her own name.

People with dementia can still lead vibrant lives, no matter their diagnosis. Yet the sharp rise of Alzheimer's and other forms of dementia is deeply concerning, especially as the population ages. More than half a million Canadians now live with some form of dementia, and 65 per cent of those diagnosed after age 65 are women. This number is expected to rise to 937,000 by 2031, according to a report from the Alzheimer Society of Canada, and combined costs to the healthcare system and to individuals will balloon to $16.6 billion. It's a similar story elsewhere.

Alzheimer's is clearly a major health challenge, if not already a crisis. Yet a cure remains elusive. Countless dollars have been spent on finding a remedy ever since German psychiatrist Dr. Alois Alzheimer first identified the disease in 1906, while billions would be saved with the right treatment. So, what's the issue?

MORE RESEARCH REQUIRED

One problem is that researchers still don't fully understand the disease, says Dr. David Tang-Wai, co-director of University Health Network (UHN) Memory Clinic at Toronto Western Hospital. "We have ideas and theories," he says. Researchers know that a brain with Alzheimer's is characterized by scattered clumps of two specific proteins, called beta-amyloid and tau, which prevent nutrients and signals from reaching brain cells. But experts don't yet have a handle on what triggers the disease in a healthy brain. "How do you go from a normal brain to the beginnings of Alzheimer's disease? We know pretty much everything after that, but what is that process?"

Without a clear understanding of the underlying biology of the illness, there isn't much chance for a cure. Meanwhile, an Alzheimer's diagnosis is an imperfect process. "Of the top 10 [causes of death] recognized by the WHO, Alzheimer's disease is the one for which we don't have a clear-cut diagnostic technique," says Dr. Donald Weaver, co-director and senior scientist at the Krembil Brain Institute, who doesn't mince words about the uphill battle dementia researchers face. "And even if we were able to diagnose it, we couldn't treat it."

TROUBLE FINDING TREATMENTS

It's not that companies haven't been trying to find a cure. Pharmaceutical businesses have poured billions into the search, and their efforts have yielded some results. Medications such as Aricept (Pfizer), Exelon (Novartis) and others symptomatically help problems with cognition, memory and the ability to do basic activities like bathing and eating. They do this by increasing the amount of the neurotransmitter acetylcholine in the brain, which tends to decline with Alzheimer's disease.

While this helps, it's far from a cure. "If you have strep throat, you can take Aspirin," says Dr. Weaver. "It will help with the pain and the fever, but you still have strep throat." What we don't have, he says, are what scientists call "disease-modifying drugs." Rather than treating the symptoms, these Holy Grail drugs would stop the pathological changes in the brain that lead to the disease in the first place. A conservative estimate is that first-year sales of such a drug would be around $10 billion. But it's a tough jackpot to win. "The last 196 trials of disease-modifying drugs have all failed," says Dr. Weaver.

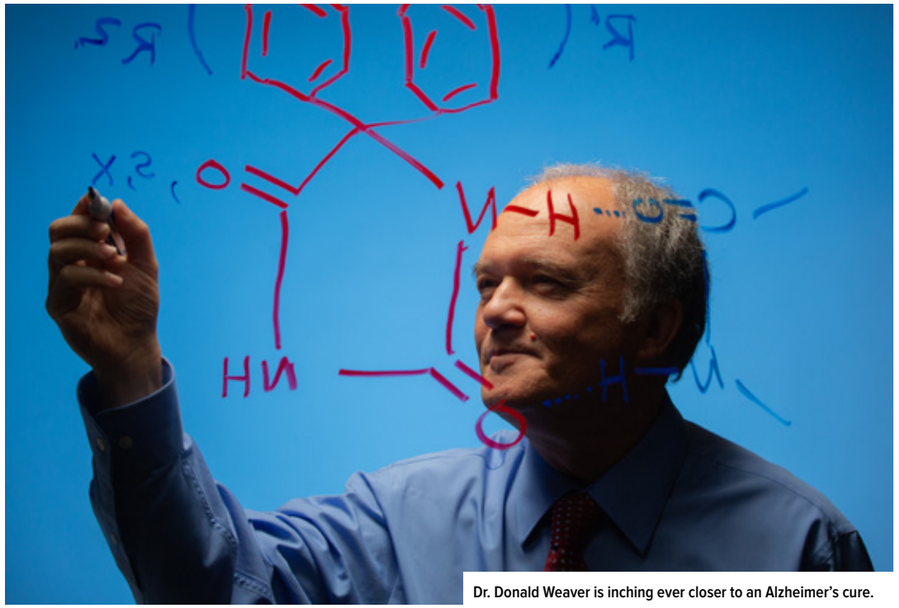
> **"Of the top 10 [causes of death] recognized by the WHO, Alzheimer's disease is the one for which we don't have a clear-cut diagnostic technique."**
>
> **Dr. Donald Weaver**
> Senior Scientist and Co-director of Krembil Brain Institute

Part of the reason for this is that while companies have worked on the right drugs, they've been working with the wrong timelines, explains Dr. Weaver. The brain is made mostly of fat, but proteins play an important role in how neurons signal to each other. For decades, Alzheimer's drug research focused on a certain protein called beta-amyloid, which forms harmful plaques when it clumps together with other proteins. These plaques are toxic, preventing nerve signalling and destroying brain cells. But the bet on beta-amyloid was flawed. "A number of people developed agents that prevent the clumping, ›

but when they were given to people, they did nothing," he says. Researchers now realize that beta-amyloid likely begins to clump, or "misfold," 20 years before patients show their first symptoms. This means the drugs might have been effective at one point, but they're two decades too late.

After so many high-profile failures, these pharmaceutical giants are now pulling the plug. Pfizer made headlines when it halted its search for new Alzheimer's and Parkinson's drugs in January 2018. In June of that same year, AstraZeneca and Eli Lilly stopped a trial of a drug intended for early-stage Alzheimer's disease. The news is devastating for patients and their families, who see drug trials as a source of hope.

There is still progress being made on a cure, however. Dr. Weaver and his colleagues are working on new possible disease-modifying drugs at Krembil – and they refuse to give up.



Dr. Donald Weaver is inching ever closer to an Alzheimer's cure.

DISCOVERING ALZHEIMER'S EARLY

What we do know about Alzheimer's, the most common type of dementia, is that affected brains look different than healthy ones. Plaques and tangles created by the clumping of beta-amyloid and tau proteins result in cell death. Brains lose tissue and shrink in size.

For many years, examining the brain post-mortem was the only way to diagnose Alzheimer's. Diagnosis is done on living patients today, but it's tricky. Doctors typically administer a test on memory, cognition and attention, which they score themselves using paper and pen – paper that will be buried in a file folder afterwards. At Krembil, Dr. Tang-Wai and a group of University of Toronto researchers are using new technology to come up with a faster, more nuanced test – one that can simultaneously gather data to lead to future discoveries.

The new Toronto Cognitive Assessment (TorCA) was developed by three principal researchers, including Dr. Tang-Wai, and other experts from geriatric medicine, geriatric psychiatry, neuropsychology and neurology. Within the 30 minutes it takes to administer the test on a tablet, the TorCA instantly compares the patient's score with that of healthy subjects in Toronto in their age group, showing a star if they're below a certain range – helping their doctor to diagnose them quicker.

More significantly, the test also does on-the-fly data capture, gathering and sharing details from patients across Toronto with researchers around the city. One of the main obstacles slowing down global Alzheimer's research is that researchers must ask subjects' permission to use their data anew with every study. The TorCA – which has been rolled out at Baycrest, CAMH, Sunnybrook and UHN – asks permission just once to store data for future research. It also removes identifying personal information. This will create a data goldmine that could lead to untold new breakthroughs. "Most of our advances in almost everything in medicine are because we study a lot of people," Dr. Tang-Wai explains.

To illustrate, take the clock test. Drawing a circular clock face is an old and simple way to screen for dementia. A correctly drawn clock is typically a sign that someone is dementia-free. What if a subject draws a perfect clock, however, but in an odd way – drawing the hands first, then adding the numbers, and finally the circle at the end? A paper test can't record this level of detail, but an electronic one can. That information would be added to a data set of other subjects in the city who also draw their clocks that same way. We'd be able to find out what else these subjects have in common – and perhaps reveal something new about the earliest, subtlest changes inside brains affected by dementia.

What we do know about Alzheimer's, the most common type of dementia, is that affected brains look different than healthy ones. These brains lose tissue, and shrink in size.

Early diagnosis helped Cairine. Her family doctor suggested she take a cognitive test in 2010 after he noticed she showed some confusion during a routine appointment, something so slight her husband hadn't picked up on it. Cairine was diagnosed with mild cognitive impairment and brought under the care of Dr. Tang-Wai and Krembil. Ultimately diagnosed with Alzheimer's, she has been taking three drugs that have collectively slowed the progression of her disease.

"I don't forget every last thing," she says. Her illness has had a "gentle slope" over years, says Henderson, giving them both time to adjust.

At Krembil, they feel they're not only plugged into the latest discoveries, but also treated with compassion, says Henderson. "Dr. Tang-Wai doesn't just focus on the drugs. You feel like you've met with a psychotherapist," he says.

FINDING A CURE

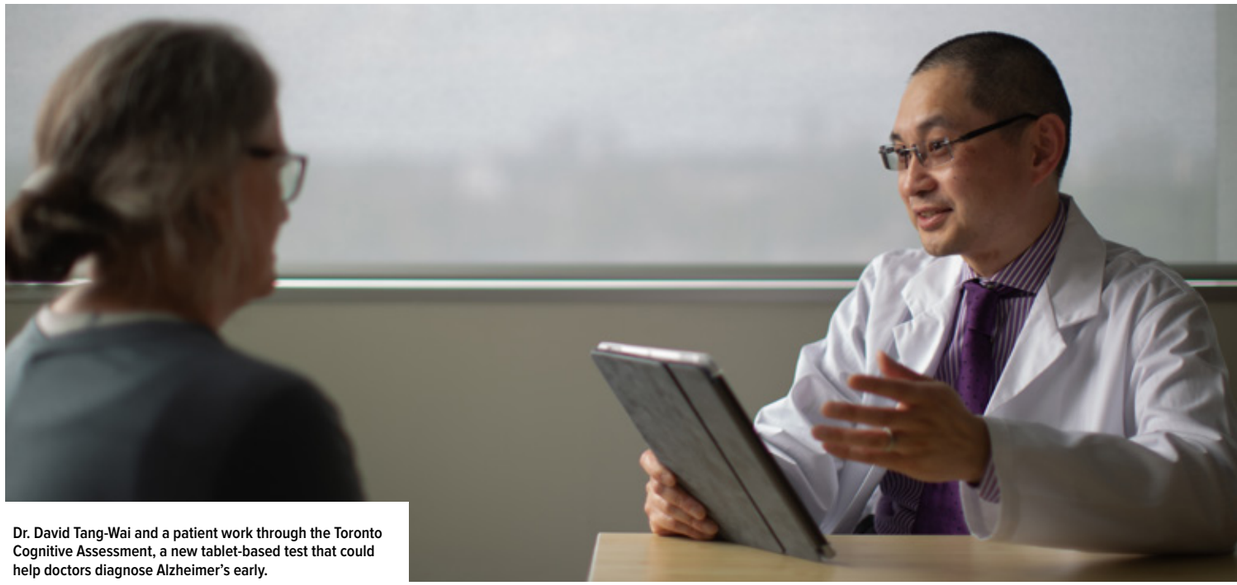
If Dr. Tang-Wai is working to diagnose patients earlier, Dr. Weaver is set on finding new medications to treat them. He acknowledges his "likelihood of failure is 99 per cent," which may be why he's working on multiple drugs at once.

While so many failed earlier trials focused solely on beta-amyloid protein, Dr. Weaver is working on a drug that will act on the tau protein. When healthy, tau transports essential nutrients in the brain; when it clumps or tangles, it prevents nutrients from being delivered and kills cells, resulting in the brain changes of Alzheimer's. Tau is promising because researchers believe it might respond to treatment even after a patient has already experienced symptoms. Dr. Weaver, who also holds a chemistry Ph.D., used computer modelling to analyze tau's distinct shape and has tested about 12 million chemical compounds to find some that can block the deadly changes in tau's shape before it does too much damage. Along with French pharmaceutical company Servier, he is working to turn the compounds he's found into drugs for the market – and for future patients.

66%
Increase in cases of dementia between today and 2031.
(Alzheimer Society of Canada)

Inflammation is another new frontier in Alzheimer's research that scientists are excited about, and Dr. Weaver is no exception. The body's inflammatory response is a key part of healing, but chronic inflammation is now thought to be the cause of many kinds of illnesses, from allergies to cancer. Inflammation may be a factor in Alzheimer's when it involves the brain's glial cells – support cells that cluster around the neurons and help them function. Although the cause is not yet clear, these support cells can change and produce toxic, inflammatory chemicals that kill neighbouring neurons. Dr. Weaver is working on a drug that will dampen the inflammatory response.

While traditional drug companies may be giving up on Alzheimer's research, doctors and researchers at Krembil certainly aren't – and neither is Cairine. Far from slowing down, she started painting recently, both abstract canvases and pictures of animals. They're neon yellows and acid pinks. She also does everything her retirement home offers, from music appreciation to dance. "I have to recognize how I am," she says. But that doesn't mean she's going to let that define her.



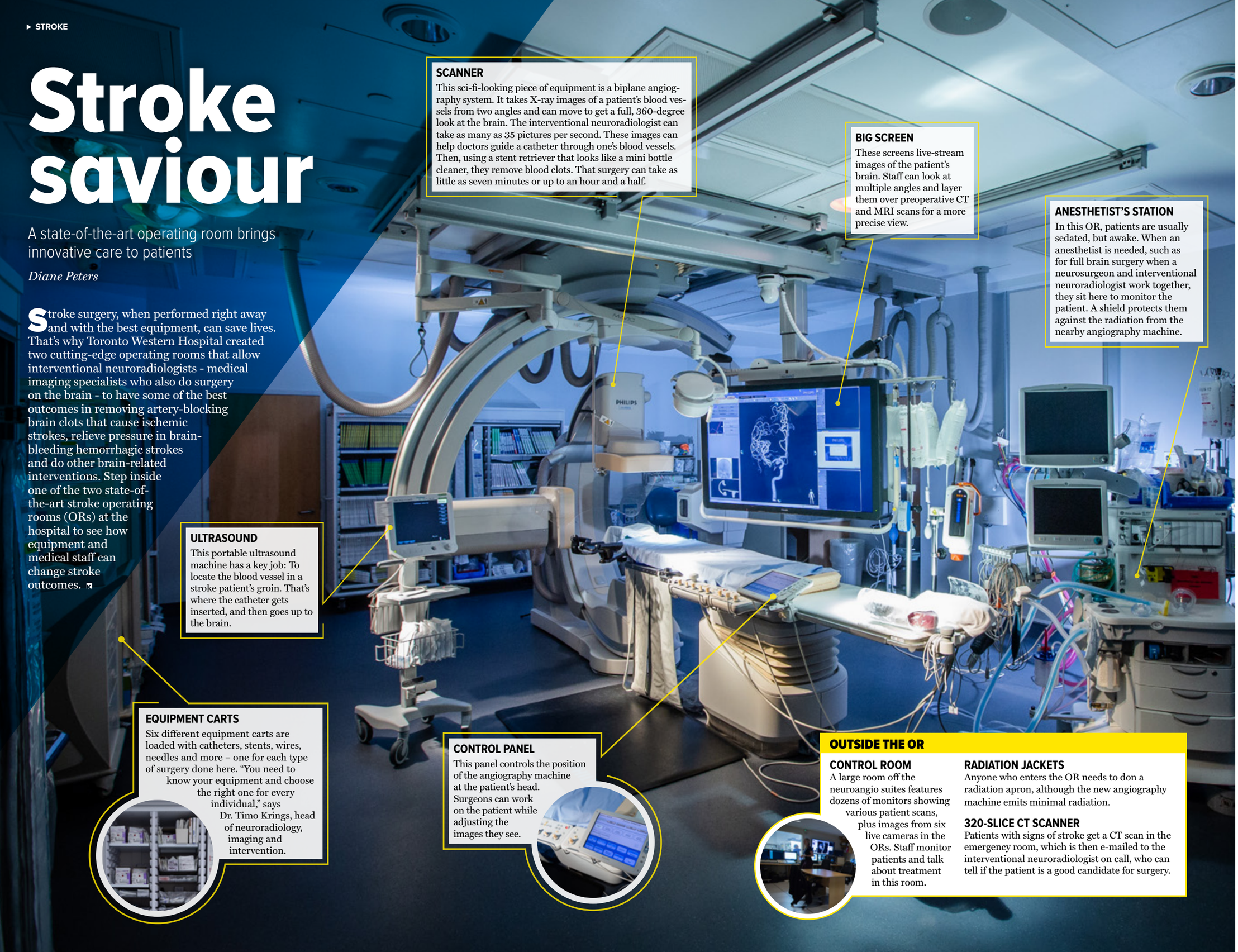
Dr. David Tang-Wai and a patient work through the Toronto Cognitive Assessment, a new tablet-based test that could help doctors diagnose Alzheimer's early.

Stroke saviour

A state-of-the-art operating room brings innovative care to patients

Diane Peters

Stroke surgery, when performed right away and with the best equipment, can save lives. That's why Toronto Western Hospital created two cutting-edge operating rooms that allow interventional neuroradiologists - medical imaging specialists who also do surgery on the brain - to have some of the best outcomes in removing artery-blocking brain clots that cause ischemic strokes, relieve pressure in brain-bleeding hemorrhagic strokes and do other brain-related interventions. Step inside one of the two state-of-the-art stroke operating rooms (ORs) at the hospital to see how equipment and medical staff can change stroke outcomes.



SCANNER
This sci-fi-looking piece of equipment is a biplane angiography system. It takes X-ray images of a patient's blood vessels from two angles and can move to get a full, 360-degree look at the brain. The interventional neuroradiologist can take as many as 35 pictures per second. These images can help doctors guide a catheter through one's blood vessels. Then, using a stent retriever that looks like a mini bottle cleaner, they remove blood clots. That surgery can take as little as seven minutes or up to an hour and a half.

BIG SCREEN
These screens live-stream images of the patient's brain. Staff can look at multiple angles and layer them over preoperative CT and MRI scans for a more precise view.

ANESTHETIST'S STATION
In this OR, patients are usually sedated, but awake. When an anesthetist is needed, such as for full brain surgery when a neurosurgeon and interventional neuroradiologist work together, they sit here to monitor the patient. A shield protects them against the radiation from the nearby angiography machine.

ULTRASOUND
This portable ultrasound machine has a key job: To locate the blood vessel in a stroke patient's groin. That's where the catheter gets inserted, and then goes up to the brain.

EQUIPMENT CARTS
Six different equipment carts are loaded with catheters, stents, wires, needles and more – one for each type of surgery done here. "You need to know your equipment and choose the right one for every individual," says Dr. Timo Krings, head of neuroradiology, imaging and intervention.

CONTROL PANEL
This panel controls the position of the angiography machine at the patient's head. Surgeons can work on the patient while adjusting the images they see.

OUTSIDE THE OR

CONTROL ROOM
A large room off the neuroangio suites features dozens of monitors showing various patient scans, plus images from six live cameras in the ORs. Staff monitor patients and talk about treatment in this room.

RADIATION JACKETS
Anyone who enters the OR needs to don a radiation apron, although the new angiography machine emits minimal radiation.

320-SLICE CT SCANNER
Patients with signs of stroke get a CT scan in the emergency room, which is then e-mailed to the interventional neuroradiologist on call, who can tell if the patient is a good candidate for surgery.

STROKE'S ALL-AGES IMPACT

Strokes don't just devastate the lives of older adults: People of any age can have them. Most often, they're caused by brain arteriovenous malformations (BAVMs), a genetic condition people are either born with or develop early in life. With this condition, some of the arteries of the brain are malformed and can bleed or rupture. "It's a bad disease, as the risk of bleeding over a lifetime is high," says Dr. Ivan Radovanovic, a Krembil Brain Institute neurosurgeon. "We don't have any drugs to treat it."

REPAIRING MALFORMATIONS
Dr. Radovanovic works with interventional neuroradiologists like Dr. Timo Krings to repair these malformations surgically. His research into the condition has found that a gene called KRAP (ki-ras-induced actin-interacting protein), which has been linked to some cancers, has a connection to BAVMs.

Existing cancer drugs might impact this disease's genetic pathway. Dr. Radovanovic is working with fellow researcher Dr. Jason Fish, also from UHN, to study preclinical models with altered KRAP genes and their response to these drugs.

MORE STUDY NEEDED
Better understanding the genetics of BAVMs could help Krembil researchers learn more about how the condition develops in the first place – and how it can lead to stroke in kids and adults. If we can find out more about the body's genetic messages, especially regarding blood vessels and their formation, many of the outstanding questions around how the brain and circulatory systems work could be answered. "We're thrilled to be addressing that in our research," says Dr. Radovanovic.

Jermaine O'Connor has been dealing with pain for years, but he's hopeful new research from Krembil will help him – and others.

Mapping the pathways of pain

Researchers haven't quite figured out what causes this feeling, but new imaging tests may help people put pain in a different perspective

Wendy Glauser

Jermaine O'Connor has struggled with pain for as long as he can remember. The Toronto-based digital marketer often has trouble moving his arms and legs – he suffers from excruciating joint pain caused by sickle cell anemia – and has been to more hospital emergency rooms than he'd like to admit. When he was younger, he struggled to keep up with his friends during gym and recess, and he often had trouble concentrating in class, and later, at work.

A few years ago, Jermaine, who is 26 – an age most people don't associate with chronic pain – started his first office job. Within the first few weeks, he developed hip pain that lasted for several months. He would just grin and bear it, in part because he thought no one would understand. "I wanted to avoid all the explanations of what I have and what I'm going through," he says.

One reason why Jermaine may feel people haven't taken his disease seriously enough is most of us think we know what it's like to experience pain. We also think chronic pain is something only older people deal with. Unlike in most of us, though, Jermaine's pain doesn't completely go away, and, to make matters more confusing, researchers still aren't sure why chronic pain persists.

It's vital Jermaine pays attention to how he feels because new pains in new areas could be a sign of a complication – or it could just be that he slept wrong. He makes note of his new pains so he can ask his specialists about them. "I'll say, 'Is this something I should pay attention to?'" As with a lot of people who deal with chronic pain, it can feel like a constant battle.

Fortunately, research is being done to create a better understanding of how pain works and where it comes from. Soon, doctors will be able to map neural signals in the brain – we'll be able to see the path pain takes in our bodies – helping to answer the many pain-related questions still outstanding.

TUNING OUT

To map those signals, researchers like Dr. Karen Davis, head, Division of Brain, Imaging and Behaviour-Systems Neuroscience at the Krembil Brain Institute, are using functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG).

Dr. Davis has spent much of her scientific career working with these imaging technologies to make the pain people like Jermaine feel – pain that's internal and invisible to others – visible in brain images.

One of Dr. Davis's landmark studies, which has helped researchers understand the relationship between the brain and pain, screens how pain interferes with people's attention. It was believed pain always disrupts concentration, but Dr. Davis found that some people can perform challenging mental tasks faster when they are prodded with a painful stimulus. She calls these people attention-dominant types, or A-types, while those who are slower at a task when in pain are called pain-dominant types, or P-types. She then discovered the A-types' minds could wander away from pain, while the P-types' could not.

Using an fMRI, Dr. Davis's lab looked at brain activity in people working on a challenging task at the same time as receiving pain stimuli. Her studies found A-types have stronger and more flexible connections between key brain areas relating to attention and sensory signals. These networks include the salience network, which responds to pain stimuli; the executive control network, which is responsible for high-level cognition; the default mode network, which can draw our minds away from immediate stimuli; and the pain modulation system, which releases neurotransmitters such as the body's internal opiates to combat pain.

What this means is A-types can better turn their attention away from pain signals and toward tasks at hand, likely because they have strong and dynamic brain connections to their internal opioid system. According to Dr. Davis, we're all on a spectrum. Some of us are clearly A- or P-types, but many of us fall somewhere in the middle.

Those with chronic pain have their salience network – the part of the brain that makes us more attentive to our discomfort – stuck in an "on" mode, even when the "mind wandering," or default mode network, is activated. "So, you can imagine, with chronic pain, they're constantly paying attention to it," Dr. Davis explains.

The brain research Dr. Davis and her students conduct is more complicated than described here. For instance, she's using machine learning algorithms to calculate patterns of brain communication among various neural pathways that represent how the brain responds to different types of pain, including the aching, inflammatory pain from a back injury, and the burning, shooting neuropathic pain that can result from nerve damage.

Dr. Davis's research – and the many studies conducted by other neuroscientists – may help us identify people whose brains are not optimally wired to combat chronic pain. Instead of a doctor only asking a patient how much pain they feel on a scale of one to 10, brain scans could show why they have chronic pain. That's useful for someone like Jermaine, who often finds it difficult to explain the kind of pain he feels. It may also lead to more understanding, less stigma and better treatment. Some people, though, are worried about these kinds of objective fMRI pain tests. They're concerned doctors, insurance companies and employers could use them as a "lie detector" against people's own subjective experiences with pain.

6 million

Canadians who suffer from some sort of chronic pain due to a neurological condition.

(Statistics Canada)

FINDING PAIN IN OUR BRAINS

While this kind of test is still too inaccurate for widespread use, fMRI scans are getting closer to revealing the brain mechanism behind how we're feeling. One of Dr. Davis's earlier studies involved people who had irritable bowel syndrome (IBS) and fibromyalgia. Medical tests such as X-rays and standard clinical MRIs weren't showing something was wrong, but fMRI scans revealed highly ›

Dr. Daniel Buchman and Dr. Karen Davis say that fMRI imaging machines will be able to make people's "invisible" pain more visible.

abnormal brain activity. For the first time, the patients felt like their pain could be truly seen by someone else. Brain imaging data "has been tremendously useful to legitimize people's pain," Dr. Davis says.

However, research conducted by Dr. Davis and her students has shown there is tremendous variability in brain activity, even for people who are experiencing similar amounts of pain. This is partly because people experience chronic pain differently – it's not just a matter of pain intensity. Pain is an individual experience and includes a complex mix of sensory qualities and emotions. There are also gender differences in how the brain is wired, and brain communication can also be different for people of different ages. fMRIs reflect all these nuances.

Dr. Daniel Buchman, a bioethicist and clinician investigator with Krembil, is concerned doctors could trust a brain scan more than how patients say they're feeling. He worries people could be required to "prove" their pain before treatment is given via an fMRI test. This could increase stigma, he says. While brain imaging research for chronic pain is important, policymakers should be more concerned with the urgent ethical issue of population-level inequalities in access to pain management, he says.

SEARCHING FOR BETTER TREATMENTS

While those ethical issues are being worked out, Dr. Davis's research continues to forge ahead. She and her team now want to see if fMRI scans can be used to suggest what treatments are likely to work.

There are numerous ways to treat pain, including drugs that interfere with pain messages sent to the brain, drugs that work on specific nervous-system chemicals and non-pharmaceutical options like physiotherapy, psychotherapy and more. By conducting brain imaging on patients before treatment, and following these patients to see which treatments worked and which didn't, and who they worked for, clinicians may be able to create "personalized" treatment approaches. "If we can prevent somebody from undergoing multiple treatments that are time-consuming, costly, exhausting and don't work, and get them more quickly to the treatment that does work, then that's great for the patient, and it's great for the healthcare system," she says.

> **"If we can prevent somebody from undergoing multiple treatments that are time-consuming, costly, exhausting and don't work – then that's great for the patient, and it's great for the healthcare system."**
>
> **Dr. Karen Davis**
> Head, Division of Brain, Imaging and Behaviour-Systems Neuroscience at the Krembil Brain Institute

As for Jermaine, he's waiting to see how this research plays out and if there may be a way to better treat, if not cure, his pain. While he has been feeling better lately, he knows the searing pain could return. In the meantime, he's speaking up for himself, telling his managers when he needs to take a break, stretch or go for a de-stressing walk. He's learned, in other words, how to make his "invisible" condition more visible to others. The fMRI research is promising, he says, as it could help doctors treat pain more holistically, with more attention being paid to how pain affects emotions and concentration. "We know chronic pain isn't solely a somatic experience," he says, meaning pain doesn't just involve the body. "Treatment should reflect that."

How artificial intelligence could unlock

Parkinson's greatest mysteries

It's been 201 years since Parkinson's disease was first described in detail. While researchers understand a lot more about it today, there's still plenty that remains unknown

Mark Mann

Jonathan Rezek first sensed that something was wrong when he froze onstage at a business conference in 2012. Normally, the affable IBM sales executive would have been in his element. He'd always thrived on the adrenalin rush of public speaking, and he could ad lib confidently without notes. But this time, instead of sharpening under pressure, he panicked.

"I was like a deer caught in the headlights. I wanted to run offstage," he says, sipping a herbal tea and recalling the experience at a Toronto café near IBM's downtown office, where he leads business development at an incubator for tech startups. For most people, a bout of stage fright wouldn't be too unusual; for Jonathan, the memory still resonates ominously – it was his first glimpse of a now-familiar foe.

Though he wouldn't get his diagnosis until two years later, that uncharacteristic spell of paralysis signalled the beginning stages of Parkinson's disease, a neurodegenerative disorder that accelerates the death of brain cells responsible for producing dopamine. Dopamine is a neurotrans- ›

Can artificial intelligence help find a Parkinson's treatment? IBM's Jonathan Rezek is hopeful that it can.

mitter that carries messages in the brain and rewards behaviour. Its absence leads to mood dysregulation and can cause anhedonia, or joylessness. Dopamine also plays a role in motor function; as it depletes, people with Parkinson's struggle to control their physical movements. It wasn't until he noticed his arm shaking after workouts that Jonathan went to his doctor. A neurological assessment led to his diagnosis, revealing the source of his anxiety and tremors. "It was surreal," says Jonathan, about first hearing the news.

ASKING AI FOR HELP

Approximately 6,600 Canadians receive a diagnosis of Parkinson's every year. The disease has no cure, and nothing stops its progression. The sole treatment addresses the main symptom of Parkinson's, involuntary shaking, not the underlying cause of the neuronal degeneration, which is still unknown. Since the death of brain cells can't be halted, doctors intervene by supplying the brain with synthetic dopamine to replace what it can no longer adequately produce or effectively process, an approach that has hardly changed since the 1960s. These dopamine-replacement drugs have significant side effects that, over time, gravely compromise a patient's quality of life.

Parkinson's remains an unsolved condition, but when Jonathan received his diagnosis in 2014, he found himself in a unique position to do something about that. In the preceding years, he'd been involved in advising IBM's customers about how to solve business problems using Watson, the company's proprietary artificial intelligence (AI) program that specializes in natural language processing, a subset of AI research that focuses on going beyond keyword searches to interpreting sentences. In 2011, Watson made its public debut on Jeopardy!, besting two of the television game show's champions. It was a breakthrough moment for AI. Watson could comprehend a question and rapidly parse millions of articles to provide a precise and accurate answer, not just a list of possibilities. Jonathan started to wonder what would happen if Watson's powers were applied to the core questions that had stymied Parkinson's researchers for decades. Could AI find a cure? Or, at least, a more effective treatment?

After his diagnosis, Jonathan felt crushed. "I was depressed for [a couple of] years. It was hard, but I eventually said, 'I'm not going to live the rest of my life this way,'" he says. Since then, Jonathan has been pushing back against the slow erosion of his dopamine-producing brain cells, forcing himself to stay motivated and engaged. At IBM, he started talking with colleagues and IBM researchers about the possibility of building relevant applications for Watson for Drug Discovery, a health care-focused facet of the Watson program. In order for that to work, Jonathan needed Parkinson's experts to join the project and teach the supercomputer what to look for.

Dr. Connie Marras, a Krembil epidemiologist and neurologist, is working with IBM's Watson to reveal some of Parkinson's still-hidden secrets.

80%

Percentage of dopamine-producing cells in the substantia nigra, an area of the brain responsible for muscle movement, which are lost in Parkinson's patients.
(Stanford University)

In 2015, Jonathan got involved with the Edmond J. Safra Program in Parkinson's Disease at Toronto Western Hospital. There, he started seeing Dr. Connie Marras, an epidemiologist and neurologist, who divides her time between research and clinical practice. At one of their meetings, Jonathan showed her the proof-of-concept work that IBM had already done with Baylor College of Medicine to find genetic targets for potential new cancer therapies. In that project, researchers gave Watson access to historical research up to a certain date, and tasked the AI software with predicting subsequent findings, which it did successfully. Having proven the approach works, researchers then gave Watson all the available data and literature and asked it for more predictions. They are currently investigating those results. Dr. Marras was impressed. "It seemed like something that would potentially be a lost opportunity if we did not pursue it," she says.

Jonathan arranged a conference call with scientists at IBM, and Dr. Marras invited two other Parkinson's researchers from the Krembil Brain Institute to join her on the call. Dr. Lorraine Kalia's research seeks to understand the molecular mechanisms that cause neuronal death in Parkinson's disease, and Dr. Naomi Visanji studies ways to mitigate the main debilitating side effect of dopamine replacement. Together with Jonathan and the IBM experts, the researchers determined that they would try using a feature of Watson for Drug Discovery called predictive analytics. In essence, Watson would look at more than 20 million research abstracts and make connections that no one had spotted before. "Watson can do this in a matter of minutes," says Dr. Kalia. Given the right inputs, the researchers hoped Watson would be able to identify potential new treatments for them to explore.

FINDING TREATMENTS FASTER

The three doctors recognized Watson could launch them past the main roadblock in Parkinson's research: Time. Parkinson's is a gradual disease, unfolding slowly over decades. Jonathan calls it a life sentence, not a death sentence. "Because it's a slow-moving progressive disease, it's hard to study," he explains. For researchers, progress can be glacial. Watson, on the other hand, is nothing if not fast. It can't do experiments, but it can digest vast troves of data at lightning speed.

Another factor slowing down the development of new treatments for Parkinson's is simply the nature of medical research itself. Namely, there's so much of it. "I stay up to date as best I can on the Parkinson's disease literature, but I can't possibly stay up to date on all of it," admits Dr. Visanji. Fortunately, Watson was designed to find signals in the noise. AI tools are essentially advanced pattern finders – where we see disparate data sets, they see constellations. Machine learning algorithms can find, for example, our tastes and appetites in our online behaviour and then try to predict our likely purchases. The researchers who embraced Jonathan's project were betting that when Watson read a few million published research summaries, it would find commonalities across diseases, identifying patterns beyond the scale the human mind can perceive.

In the interest of helping patients like Jonathan sooner rather than later, the three researchers decided to pursue what they call a drug-repurposing strategy. Rather than look for a compound that could be developed into a new drug – an expensive process that takes upward of a decade to complete and frequently fails – they'd instead try to find an existing drug with some unappreciated value in affecting neurodegeneration. "Because they've gone through the hurdles of approval, you at least know these drugs are safe for humans," explains Dr. Kalia. The most famous example of a repurposed drug is Viagra, which was originally used to treat ›

Jonathan started to wonder what would happen if Watson's powers were applied to the core questions that had stymied Parkinson's researchers for decades. Could AI find a cure?

hypertension. Researchers working with Watson hoped to replicate such a success with Parkinson's. If they found an existing drug with some unrecognized utility, they could get it to patients much sooner.

PURSUING HARD-TO-FIND PATTERNS

Dr. Kalia's research team decided to ask Watson for leads on existing drugs that might affect the underlying cause of neurodegeneration in Parkinson's.

Dr. Visanji and other researchers focused on finding drugs to mitigate the main side effect of dopamine-replacement therapy, a condition called dyskinesia, which refers to the twitchy, writhing movements most people associate with the disease. Once the researchers formulated their inquiries, Jonathan obtained funding for them from the Ontario Brain Institute so they could spend the necessary time to teach Watson what to look for in the literature. "We have to make absolutely sure we're training Watson well, and that we're giving it the right information," says Dr. Marras.

The researchers provided Watson with a list of chemical compounds that have been demonstrated to have a positive effect in some aspect of Parkinson's treatment, but have never been fully developed into marketable pharmaceuticals. They then gave Watson a list of drugs that are already approved for use in humans. Watson compared the two, hunting for any drug that had a fingerprint similar to the training compounds. If Watson can see what works in drugs that aren't fit for consumption, it can look for the same traits in drugs available for humans. "It's almost like forced serendipity," says Jonathan.

It took months to plan and set up the two projects, and minutes for Watson to do the work. In the end, Watson provided both research projects a ranked list of likely candidates. Some were drugs they expected to see, and that was a good thing, because it demonstrated that Watson understood the problem and was on the right track, says Dr. Kalia. Others on the list were unexpected. "There were many surprises," says Dr. Visanji. "These were the drugs we got most excited about, because that's what we wanted Watson to do. We wanted it to find the needle in the haystack that we couldn't see."

Unfortunately, the algorithms Watson uses to identify these potential treatments are so complex that it's difficult for researchers to retrace its steps. They'll never be able to reverse-engineer Watson's conclusions to tell a clear story about how it found the patterns in the research that it did. Therefore, to take the next step, the Parkinson's researchers needed to make a leap of faith and test highly ranked drugs in the laboratory. Dr. Visanji's team tested one of Watson's surprising hypotheses and found that it worked to prevent dyskinesia, though it also made the Parkinson's slightly worse. "Still, the fact that it worked was huge. And I don't know how we ever would have come up with this idea otherwise," she says. With this promising finding in hand, Dr. Visanji and her team obtained funding to perform further laboratory tests on four more of Watson's suggestions.

MORE FUNDING NEEDED

As promising as AI may be, it continues to face skepticism from the research community because it's still unproven.

Dr. Marras and Dr. Kalia haven't been able to find funding to test their Watson-derived hypotheses for treating the underlying causes of neurodegeneration in Parkinson's. "Watson has given us new hypotheses, but there's not a lot of credence in its value until we do the validation," says Dr. Marras.

For his part, Jonathan is managing his symptoms as best he can – he exercises frequently on his at-home rowing machine – and he's hoping that better treatments will come from the research Watson has enabled. In the meantime, he's focused on doing everything he can, through his role at IBM, to make Watson ubiquitous, including offering discount pricing for academics.

Jonathan believes that AI will one day be as commonplace as a microscope. Using Watson to hunt for patterns across the entirety of medical literature represents a whole new way of doing research, and it could give doctors a reliable shortcut to accelerate advances and discoveries. All they need from Watson is a few smart ideas. "If there's one or two hits in there that lead us down a new pathway or area of investigation, that in itself will have value," says Dr. Kalia. We're only at the beginning of AI-enabled medical research, but at this rate, we won't be for long.

Dr. Lorraine Kalia is hopeful AI will reveal treatments that haven't been considered before.

We asked Isabelle Siciliano to sum up life with epilepsy. The phrase above her is how she feels, in her own words.

Finding acceptance in epilepsy

One of the main drawbacks of epilepsy is the stigma that comes with having the disorder

Diane Peters

In 2004, when Isabelle Siciliano was 13, she woke up in the middle of the night to a loud commotion and family members hovering over her bed. "I felt nauseous and very disoriented," she recalls.

She'd had a seizure. After a series of medical tests, Isabelle received a life-changing diagnosis: She had tuberous sclerosis, a genetic condition that causes mostly benign tumours inside the body.

Isabelle, now 27, had one tumour on her heart, which has since gone away, and still has them on her kidneys. She can still develop growths on her lungs, and she risks passing the condition on to future children. But most troubling of all is that tumours in her brain cause nerves to misfire, creating seizures.

When someone has regular seizures like this, they're considered to have epilepsy. Epilepsy can be caused by genetic factors, like in Isabelle's case, or it can be caused by brain injury, cancer, stroke or other unknown reasons. While the other aspects of her original diagnosis worry her, it's the epilepsy that impacts Isabelle's life every day. She takes medication but can never drive. She goes to bed at 8 p.m., or risks the possibility of sleep deprivation causing more seizures. "Even stress itself can be a trigger," says the Toronto-based theatre educator.

In her early 20s, Isabelle developed severe anxiety. That's partly because of what happens in the brain when a seizure occurs – doctors think that the process of nerves misfiring can create anxiety in itself – but it's also because of the stigma associated with epilepsy. According to a 2008 study from the *Canadian Journal of Neurological Sciences*, people with epilepsy are often "wrongly viewed as having mental health and antisocial ›

issues and as being potentially violent toward others," and, say the authors of the report, "they fear rejection and often feel shame or loneliness from this diagnosis."

While epilepsy has been around for centuries, few know it's one of the most common neurological diseases in the world, impacting an estimated 350,000 Canadians, and 50 million people worldwide. "I'm sure everyone knows someone who has it, but they just don't know who," says Dr. Danielle Andrade, medical director of the Krembil Brain Institute's Epilepsy Program.

Silence has led to a lack of understanding. "Every time I disclose that I have epilepsy, I am fast to say, 'Don't worry – you might be thinking I'm going to drop down on the ground and convulse, but I'm not going to do that.'" says Isabelle. These attitudes have made it harder for researchers to attract generous charitable donations and land big government research dollars.

At Krembil, though, work is underway to change the lives of people with the disorder, including their treatment and how they're viewed by the public. With a patient base of 2,000, one of the largest in the world, Dr. Andrade and her team are doing much-needed work on the genetics of the disease and using new cutting-edge technology to better understand seizures and improve brain surgery outcomes.

They're also educating the public about this misunderstood disorder to push against stereotypes and encourage more interest in research. "We want to reduce the stigma, but at the same time we want people to remember this is a serious disease," says Dr. Richard Wennberg, clinical neurophysiologist and researcher with Krembil and a member of the epilepsy team.

THE ROOTS OF STIGMA

Reactions to this disorder range from ignorance to prejudice. While Isabelle has found full support at work, doctors at Krembil often hear of their patients facing discrimination. Elsewhere, it's worse. "In some countries, the stigma can affect the whole family and [epilepsy can] be considered a curse,"

> **"Every time I disclose that I have epilepsy, I am fast to say, 'Don't worry – you might be thinking I'm going to drop down on the ground and convulse, but I'm not going to do that.'"**
>
> **Isabelle Siciliano**
> Krembil Brain Institute patient

Dr. Danielle Andrade, medical director of Krembil's Epilepsy Program, is working with state-of-the-art technology to learn more about why seizures occur.

says Dr. James Eubanks, a senior scientist at Krembil.

One misconception is that all seizures are like ones you see on TV. While Isabelle used to have tonic-clonic seizures – formerly called grand mal, the kind in which you convulse – she now has focal seizures, which are almost invisible. "I could be sitting here talking to you, but I could feel like I am being separated from my body."

She sometimes forgets words or slurs her speech during these quick episodes. "You may look like you are intoxicated during or right after a seizure," adds Dr. Andrade, who recommends that all her patients wear medical alert bracelets, which Isabelle does, so people won't make false assumptions.

BETTER TREATMENTS

Patients with epilepsy want a better understanding of their disorder, not just by society, but by medical science. For starters, they need better treatment options. There are 14 drugs approved to treat epilepsy in Canada, but no way to know which one will work on any given patient. "Treating epilepsy with medications is sometimes hit-or-miss," says Dr. Eubanks, as doctors can't tell in advance which prescription will work on specific patients.

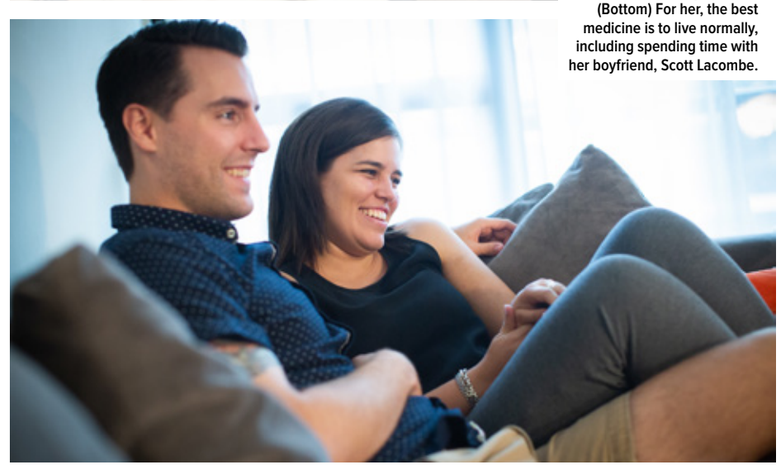
More research on genetics might help: About 70 per cent of epilepsies have a genetic cause, which could help with linking the right drugs to patients and assist in finding new medications. Over the last 10 years, researchers have identified more than 500 genes connected to the disorder. "We know there are many more to be found, and we are working on that," says Dr. Andrade.

For instance, the Adult Epilepsy Genetics Program at Toronto Western Hospital (TWH) discovered a gene connected to sudden unexpected death in epilepsy (SUDEP), a rare phenomenon that happens to about one in 1,000 people with the disorder during or after a seizure. Before finding this gene, doctors had no way of predicting who was at risk for SUDEP in patients with moderate seizure control. This is because SUDEP often happens to people with frequent and severe seizures, but it can occur in some people who have relatively mild cases of epilepsy. Now that the gene has been identified, doctors at Krembil can screen epilepsy patients for it to find out if they are at risk and ensure that those people stick to their medication regime.

At a higher level, Dr. Eubanks wants to better understand how a genetic mutation impacts cells and leads to disease. He's currently working with the gene CDKL5, mutations of which cause a very severe form of epilepsy. "We're trying to fill in the missing parts of the map," he says.

30% – 40%

Percentage of people with intractable epilepsy – seizures that cannot be controlled by current treatments.
(National Institute of Neurological Disorders and Stroke)



(Top) Isabelle, at work with a friend, leads the same kind of life as everyone else. (Bottom) For her, the best medicine is to live normally, including spending time with her boyfriend, Scott Lacombe.

A LEAP IN TESTING

Another area in epilepsy with serious gaps is related to seizures themselves. Dr. Wennberg, the Krembil clinical researcher, is using TWH's magnetoencephalography (MEG) machine – acquired thanks to philanthropic support from Mitchell Goldhar – to measure brain activity during seizures. Doctors test patients with epilepsy after they've been sleep-deprived so that they'll nod off and have seizures. He says the hospital has measured more actual seizures in the MEG than any other organization in the world. Working with a mathematician, Dr. Luis Garcia Dominguez, the doctors can isolate brain activity using MEG and closely track a seizure's signals to understand where and how they happen.

MEG has another practical function: It can reduce the number of surgeries people need to eliminate seizures. For the 30 per cent of epilepsy patients who don't respond to medication, surgery can reduce or even get rid of seizures. Even some patients who can control their condition by medication will consider surgery, since they can then stop taking medications, many of which come with side effects.

Surgery, of course, is intrusive and involves removing the parts of the brain that cause seizures. For those who have a choice of surgery, the decision to go ahead with an operation is a difficult one. Currently, to assess whether someone is a good candidate for surgery, they may need to be monitored by electroencephalography (EEG), where electrodes are placed in the brain to pinpoint tissue that needs to be removed. That procedure is invasive, too. If they can have surgery, they need to assess whether the risks – memory problems, behavioural changes and vision issues are the big ones – are worth it.

While choosing to have brain surgery will always be a tough decision, MEG may help do away with EEG implants, which will then make the procedure that much less invasive, says Dr. Wennberg. Using MEG, he can overlay the neurophysiologic results with existing scans of the patient's brain to create a more precise map. "We are pushing the envelope further with the accuracy we get," he says.

In 2016, Isabelle went through a lengthy surgery assessment process that included spending 12 days in TWH's monitoring unit, where she found out she is a candidate for surgery. Using MEG, doctors were able to localize her epilepsy to the edge of one of her brain tumours.

For now, though, she has decided to put off surgery. She wants to focus on work, and she also hopes the cutting-edge research Krembil is doing will reduce the need for an operation. At some point, she may get access to better drugs with fewer side effects, for instance.

In the meantime, she has joined a surgery support group at TWH, because she wants to get as many perspectives as possible. But the priority for now is on living her life. "I am putting surgery aside for the moment," she says. "I am focusing on work right now, as it's hard to focus on both."

Dr. Charles Tator is taking a three-pronged approach to help reduce the number of concussions in Canadians.

Putting a halt to head hits

Combatting concussions through research, education and policy

Claire Gagne

39%

Percentage of children aged 10 to 18 who have visited an emergency room for a sports-related head injury and were diagnosed with a concussion.
(Government of Canada)

Concussions are a serious issue in sport. According to the National Football League, 13.5 per cent more concussions were reported among its players in 2017 over the year before, while Blue Cross Blue Shield found a 43 per cent increase in sports-related concussions between 2010 and 2015. That's not a surprise to Dr. Charles Tator, director of the Canadian Concussion Centre, an organization based out of the Krembil Brain Institute that conducts concussion-related research. "There's still a lack of awareness and lack of recognition around concussions," he says. "We want to change that."

Dr. Tator has made it his mission to reduce the number of concussions in Canada, but unlike other doctors who mostly focus on science, he's taking a three-pronged approach to his work: Research, education and policy change. Since researchers are just starting to learn how concussions work, it could take time before any treatment is found. That's why he wants to change laws and raise awareness of what can happen when someone gets hit in the head.

GETTING POLICY PASSED

So far, Dr. Tator and his team have made progress in all three areas. In March, the Ontario government passed Rowan's Law, named after 17-year-old Rowan Stringer who died in 2013 after suffering two concussions within a week. Dr. Tator, among others, helped lobby the government to pass it.

The law states states that hockey coaches must oversee player safety, while organizations need to develop protocols for the removal and re-entry of a player into a game after a hit to the head has occurred. He hopes other provinces will adopt this, too. "That's the plan," he says. "To have it spread across the country."

DONATING BRAINS TO RESEARCH

On the research side, the Canadian Concussion Centre recently made headlines after it received commitments from four female athletes – Olympic skier Kerrin Lee-Gartner, hockey legends Cassie Campbell-Pascall and Fran Rider, and rugby star Jen Kish – to receive their brains after they pass away.

This is a coup, because, so far, the Centre has only received brains from male athletes. Since concussion symptoms can be worse in women, and last longer, than in men, doctors need the brains of female athletes to fully understand the damage concussions can do, says Dr. Tator.

Ideally, by studying the brains of deceased athletes, and monitoring the health of still-living ones – the Centre is doing regular tests on more than 100 Canadian Football League alumni – doctors will be able to help people prevent brain damage before it's too late.

LOOKING FOR A TREATMENT

To that end, Dr. Carmela Tartaglia, a neurologist at Krembil, and the Marion and Gerald Soloway Chair in Brain Injury and Concussion Research, is looking at the abnormal buildup of a protein called phosphorylated tau or p-tau in the brain. It's linked to the development of chronic traumatic encephalopathy (CTE), a neurodegenerative disease that has been found in former athletes like boxers or football players, who have sustained multiple hits to the head over time.

She's trying to detect abnormal tau and its effects on the brain by combining information from p-tau imaging tests and cerebrospinal fluid, genetics, eye tracking and neuropsychological assessments. "We want to say your brain is vulnerable to concussions and you cannot afford to get any more," she says.

While the Centre may be tackling the concussion issue from various sides – Dr. Tator is also working with Ontario's Ministry of Education to study concussion education – whether it's policy, education or research, the goal is the same: To keep brains safe. "Our duty is to the research, but it can't just be that," he says. "We need to be at the centre of this and shaping those around us."

The mission to save minds

Mark Krembil, president of the Krembil Foundation, on why his family gives to brain research

Renee Sylvestre-Williams

You might be surprised to find the brain has traditionally taken a back seat to other research areas when it comes to funding. While the brain may be the organ that makes us tick, other important areas such as cancer and cardiac have received proportionally more funding over the years. In 2000, Mark Krembil noticed that our most important organ wasn't getting the attention it deserved and decided to make the brain a major focus at the Krembil Foundation. Since then, the Foundation has been a major brain research donor in Canada and, Mr. Krembil says, it will keep supporting brain research as long as there is need. We asked him why he is so interested in the brain, how technology is changing the way doctors work and what his peers can do to step up their own giving.

HOW DO YOU THINK YOUR CONTRIBUTIONS, AND OTHER PEOPLE'S DONATIONS, HAVE HELPED?

I started looking at the brain in 2000, and since then our understanding has advanced dramatically. We understand much more about brain cellular chemistry and plasticity, how it changes and how sometimes it can even heal itself. Despite these advances we have only just scratched the surface. Before we can develop therapies for people suffering from these terrible conditions much more needs to be discovered.

FOR ALL THE SUCCESSES THERE HAVE ALSO BEEN A LOT OF FAILURES. WHAT CAN WE TAKE FROM THAT?

It is true – for example, a disease such as Alzheimer's has had many clinical trial failures – however, failure is part of learning and with each failure we learn a little bit more about what is happening in the brain. The Foundation focuses on basic research in hopes of discovering fundamental biological building blocks that can be used to develop therapies.

TECHNOLOGY AND MEDICINE ARE RAPIDLY CONVERGING. HOW WILL THAT IMPACT BRAIN RESEARCH?

The brain consists of trillions of connections, and while traditional scientific research has helped us start to understand the brain better, researchers need new tools and techniques to ensure their progress continues. This is where technology comes in. Informatics and artificial intelligence are exciting new technologies that are starting to help researchers interpret the brain and advance our understanding of how it works.

HOW HAS MEDICAL-RELATED PHILANTHROPY CHANGED?

Traditionally, philanthropy helped researchers by adding to the infrastructure that supported scientific projects and recruitment, such as institutional bricks and mortar gifts and scientific equipment. While this kind of support still plays an important role, what is lacking is increased funding for basic scientific inquiry at all levels, from the multi-million dollar team projects to the single researcher-driven basic projects.

WHAT DO YOU SAY TO YOUR PEERS WHO MIGHT NOT BE GIVING BACK?

This is a difficult question, as I prefer to lead by example rather than tell others what to do. I believe in helping people and would encourage others to do the same. We have chosen to help others by partnering with researchers in their quest to understand the human brain with the goal and hope that this information will lead to new solutions and therapies for those suffering brain disease. When it comes to giving, I would encourage others to follow their passion.

WHAT MAKES YOU…YOU?

How do you preserve memory?
Stop seizures?
Reverse paralysis?
Prevent stroke?
Manage brain tumours?

Science doesn't have these answers. Yet.
But we will be the ones to find out.

Krembil Brain Institute. Using our brains to save yours.

Support the Krembil Brain Institute at tgwhf.ca/KBI

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