UNLOCKING THE BRAIN’S BIGGEST MYSTERIES

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

INSIDE KREMBIL BRAIN INSTITUTE

100+ Neurosurgeons, neurologists, neuroradiologists, neuroanesthesiologists, neuropsychologists, neuromuscinologists 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)

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)

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

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

$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 Centre 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.

A TEAM EFFORT
Industry
Development of neuromodulation devices in humans
Rehabilitation sciences
Mathematics
Engineering

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

2018
747,000 Canadians living with dementia

2031
997,000 Canadians living with dementia
an increase of 66%

18.9%
Percentage of Canadians over age 18 suffering from chronic pain

50%
Percentage of Canadians who will have or have had a mental illness by age 40*

CONDITIONS THAT CAN BE TREATED
Parkinson’s
Epilepsy
Stroke
Spinal cord injury
Alzheimer’s and dementia
Depression
Chronic pain

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 2003, 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.

WHAT DOES rTMS WORK SO EFFECTIVELY TO TREAT A RANGE OF PSYCHOLOGICAL 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?
The technology has been slow to catch on – it requires lengthy treatments, 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.

WHAT DOES THAT MEAN FOR PATIENTS?

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 what to operate and what research studies can help improve.

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.

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

Dr. Mojgan Hodaie, founder of the non-profit NEURONproject, says that’s changing.

“Better training assists them in helping their people and their communities.”

Krembil’s NEURONproject is training the next generation of neurosurgeons around the globe.
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 indi-

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 about 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 Ariept (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, uphill battle.

“The last 196 trials of disease-modifying drugs have all failed,” says Dr. Weaver.

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...
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.

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 and attention, which they score with that of healthy 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.

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’s 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 study tau’s 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. 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 dancing. “I have to recognize how I am,” she says. But that doesn’t mean she’s going to let that define her.
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 to perform some of the best outcomes in removing artery-blocking clots and treating bleeding hemorrhagic strokes, relieve pressure in brain-stroke patients, and with the best equipment, can save lives.

That’s why Toronto Western Hospital created two state-of-the-art stroke operating rooms (ORs) at the hospital to see how medical staff can change stroke outcomes.

Scans

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 15 pictures per second. These images can help doctors guide a cathether 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.

Interventional neuroradiologists

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

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.

Ultrasound

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

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

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.

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.

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.

Radiation jackets

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

Repairing malformations

Dr. Radovanovic works with interventional neuroradiologists 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.

Strokes

Strokes don’t just devastate the lives of older adults. People of any age can have them. Most often, they’re caused by brain aneurysms and intracerebral hemorrhages (ICH), a genetic condition that 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.”

More stroke needed

Dr. Jason Fish, also from UHN, to study preclinical models with altered KRAP genes and their response to these drugs.
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.

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 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,” he says,”—and, to make matters more confusing, researchers still aren’t sure why chronic pain persists.

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, 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.

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

[Statistics Canada]
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.

Dr. Karen Davis, Head, Division of Brain, Imaging and Behaviour-Systems Neuroscience at the Krembil Brain Institute, says 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 those 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.

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.”

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 adrenaline 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 accelerating the death of brain cells responsible for producing dopamine. Dopamine is a neurotransmitter that plays an important role in how the brain processes movement and balance. 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 is hopeful that it can. Can artificial intelligence help find a Parkinson’s treatment? IBM’s Dr. Daniel Buchman and Dr. Karen Davis say that fMRI imaging machines will be able to make people’s “invisible” pain more visible.
matter that carries messages in the brain and rewards Watson. 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. Thesedopamine-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 Parkinson’s diagnosis in 2014, he found himself in a unique position to do something about it. 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 interpret 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 researchers determined that they would try using a feature of Watson 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 with a lot more speed.

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 but 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,” admires Dr. Visanji. Fortunately, Watson was designed to find signals in the noise. AI tools are especially 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 behavior 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?

hysteria 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 data. 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 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 evidence 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.”

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 2006 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, says 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,” says Dr. James Eubanks, a neurologist and researcher with Krembil.

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.’”

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 so few to 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. While Isabelle has found full support at work, doctors at Krembil often hear of their patients facing discrimination. “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 seizures in patients with 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. That 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 regimen.

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.

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’re not 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 do not 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. Isabelle has spent hours assessing whether someone is a good candidate for surgery, they may need to be monitored through 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 certain treatment problems, behavioral 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 neurophysiological results with existing scans of the patient’s brain to create a more precise map. “We are pushing the ever forward 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. Danielle Andrade, medical director of Krembil’s Epilepsy Program, is working with state-of-the-art technology to learn more about why seizures occur.
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.

GETTING POLICY PASSED
So far, Dr. Tator and his team have made progress in all three areas. In March, the Ontario government passed Rowe’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 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 Bider, 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 Maron and Gerald Solomon 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.

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.
WHAT MAKES YOU...YOU?


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.

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