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 ›

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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."

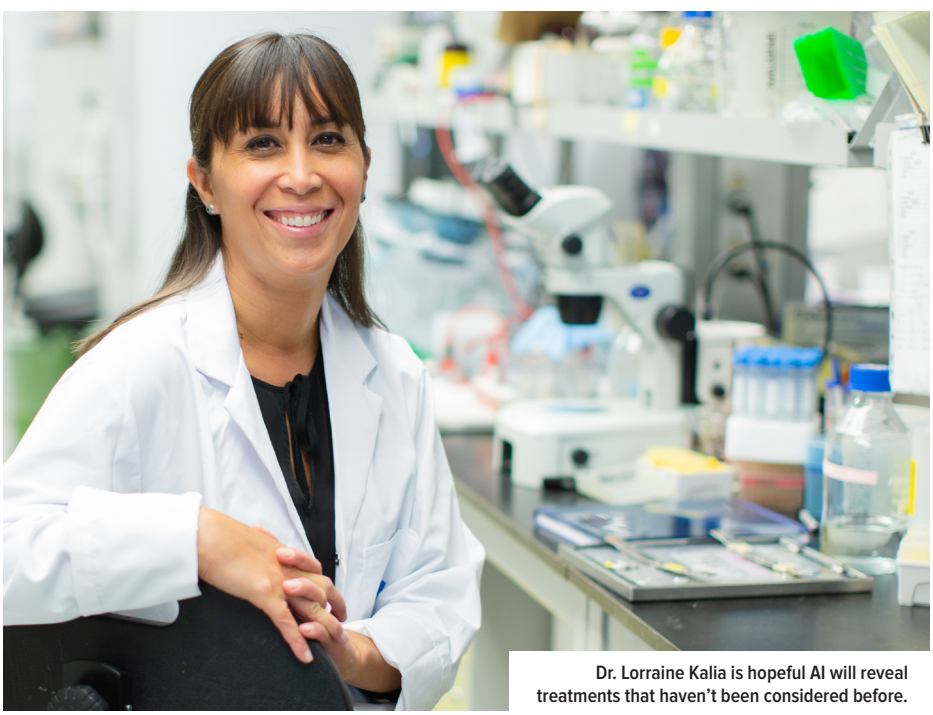
Unfortunately, the algorithms Watson uses to identify these potential treatments are so complex that it's difficult for researchers to retrace its steps. They'll never be able to reverse-engineer Watson's conclusions to tell a clear story about how it found the patterns in the research that it did. Therefore, 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.