

Dr. Kalia 0:00

[Your Complex Brain theme music] After having done this operation hundreds and hundreds of times, that moment that you turn on the stimulator and you see a tremor disappear or Parkinson's symptoms improve to five or 10 years ago in an instant, never grows tiring for me.

Heather 0:21

[theme music continues] This is Your Complex Brain, a podcast all about the brain, the diseases that impact it, and the path to finding cures. I'm your host, Heather Sherman, and I have the great pleasure of working alongside the team at the Krembil Brain Institute in Toronto, Canada, a leader in brain research and patient care. In each episode, we'll take you behind the scenes into our clinics and research labs to meet the game changers of the future. We'll also empower you with the latest research to help you take charge of your own health. You'll hear directly from people who are living with brain disease, as well as their loved ones and the care teams who support them. Join us on a journey to unravel the mystery of your complex brain. [theme music fades out]

[gentle, electronic music] Today, we're talking about deep brain stimulation, a complex brain surgery in which electrodes are placed at strategic predetermined targets within a patient's brain. The electrodes are then connected to a battery pack, which is surgically inserted under the skin of the chest, kind of like a pacemaker. For many patients living with Parkinson's disease and other neurological disorders, deep brain stimulation, also known as DBS, can be a game changer. But, DBS is not always the answer, and doctors and researchers at the Krembil Brain Institute are working hard to improve and personalize the technology to be able to help as many patients as possible. More on that later in today's episode.

First, we'd like you to meet Harry Forestell, a familiar face in Canadian media. Harry is a respected, long-time journalist, and currently the host of CBC's suppertime newscast in New Brunswick. Harry was 53 years old when he was diagnosed with Parkinson's and referred to the Movement Disorders Clinic at the Krembil Brain Institute, a world-leading team that performs more DBS surgeries than anywhere else in Canada. After meeting with Harry, the team determined that he was a candidate for the DBS surgery, which he had in September of 2022. Here's Harry's story in his own words. [gentle, electronic music continues then fades out]

Harry Forestell 2:48

[light, bubbly, electronic music] My name is Harry Forestell. I am a journalist with CBC Television. I've been a reporter and producer and host for about 35 years. It was about in 2013, the year my mother passed away, that I began to notice a tremor in my right hand. I'm left-handed so it didn't bother me that much, but it was noticeable, and it was something that I thought, "Hmm, have to have that checked out," so the next time I was at the doctor, I did. My doctor, at the time, was uncertain what it was, whether it was something called essential tremor, which I'd never heard of, but it sounded pretty benign, or whether it was something more serious, like MS, ALS, or Parkinson's. So, that was a bit of a worry. It took over the next two years to confirm the diagnosis as Parkinson's, and in that time, my neurologist in New Brunswick had referred me to Dr. Tony Lang and the team at Toronto Western Hospital Movement Disorder Clinic, and that was where, in 2015, I really had my diagnosis confirmed as Parkinson's. [light, bubbly, electronic music continues]

My symptoms at the time were mostly the tremor, and I was shaking in my left leg a lot at work. Now, I was always a leg shaker as a means of expending excess energy, I guess, when I was young, so that didn't really worry me, but it was noticeable that I was doing it when I wasn't really intending for it to happen. And then, the thing that really sort of blew my mind and frustrated me was that I was finding it

was taking more and more focus and attention just to walk normally. [light, bubbly electronic music fades out] Now, I live on a hill of quite a grade, and walking up the hill after dropping my daughter at school became a real task because I was so focused on swinging my arms in time to the movement of my legs, and I thought, "This can't be right. It shouldn't take this much time and attention. I'm just walking. It's very simple. Why is it so hard?" and that was what really was beginning to annoy and disconcert me.

[light, bubbly electronic music] The team at Toronto Western was very, very supportive, and they were very thoughtful and concerned about not just me as a patient, but about my career, what I did for a living, and knowing that I had to appear on television on a regular basis and knowing that I still had some career ahead of me—you know, I was only 53, 54 years old and I still had career ahead of me to go—and Dr. Lang said, "Don't worry. We'll get you back on air. It'll be okay." So, he was very reassuring. Nonetheless, the symptoms continued to grow and that was dispiriting. However, I did notice that the use of drugs like Levodopa, especially, was huge, in terms of helping me deal with the symptoms and control them. But over time, as my volume of Levodopa increased, the side effects of that, especially dyskinesia, began to be more and more of a factor in my mental health and my physical health.

Dyskinesia is the side effect that comes from Levodopa. Levodopa is a precursor drug. When it gets into the body, the brain transforms it into dopamine, which is a critical neurotransmitter that helps smoothly relay messages from the brain to muscle groups and parts of the body like the legs and arms. Dyskinesia is a side effect of Levodopa that causes your body to twist and torque in a very fluid fashion, so it isn't like the tremors of Parkinson's, but you will notice people who are being treated for Parkinson's, very often, their head will move, their shoulders will glide around. It's very difficult to stay still. [up-tempo electronic music] I had heard sometime earlier that there was a thing called deep brain stimulation, and I understood the broad principles of it, but I thought, "Brain surgery sounds pretty serious, and it's nothing that I want to get into right now," and as we discussed it, Dr. Lang said, "You know, we've got to see whether you would qualify for it or not," and as my symptoms grew more serious, it became more apparent to me that maybe DBS would be, you know, a more appropriate solution, a longer-term solution, and a more satisfactory solution.

I spent a weekend in November, about two years ago, going through to see if I would be a satisfactory candidate, and much to my pleasure and surprise, I passed, I guess for lack of a better phrase. [chuckles lightly] I was delighted with that, to have that prospect of another option, rather than just continuing with the growing volume of oral drugs. But, a year later, then came the opportunity to actually have the procedure done. I went up to Toronto. I was there for about a month. I was impressed and surprised by how quickly and how little fuss was involved in what had always seemed to me to be as complicated as brain surgery. [upbeat electronic music fades out] I was quite chatty, apparently. Dr. Fasano and Dr. Kalia both remarked on how my line of questioning throughout the operation surprised them a little bit. When they're doing brain surgery, they're more used to speaking to one another than they are, I think, answering questions and being interrogated by the patient, but I was curious about what was going on.

[hopeful electronic music] The recovery was very quick. I was at a hospital within 36 hours with my implant and the neurotransmitter in my chest and all the wires connected and everything ready to go, but they wanted me to heal up, of course. I spent, I think, three weeks in recovery in Toronto on my own. That all happened from the end of September to the end of October. On December 6th, I returned to Toronto and spent a week there. I had the device turned on. I was not alone. I was in front of a bevy of clinicians when it was turned on, and the effect was immediate and very, very pleasing. My tremors,

my shakes abated completely, with the bonus that it didn't have to experience the dyskinesia that goes along with the increasing doses of Levodopa, and that was a real life changer.

So since then, I came home to New Brunswick. I've had, I think, three sessions with the DBS clinical team to set the device because it very much involves a fair amount of tweaking here and there to ensure that it delivers the best result that is possible. [hopeful electronic music fades out]

The use of DBS has allowed me to return to work, not only to work in the office, but in front of the camera, which is a huge bonus for me, and I can't say enough about how it has returned my life to me. [pensive electronic music] I subsequently did a story on my treatment and included in it an illustration of me turning off my DBS and turning it back on, and I recorded that with a colleague of mine at work, and then I sat down and watch the edited video that he put together. And, [chuckling lightly] even though it was me, even though I recorded it and knew what I was doing, and even though I knew what was coming, it was a very emotional moment for me to see how vulnerable I am without DBS. The fact of the matter is that video has probably gone around the world and has just led to an avalanche of inquiries and encouragement and good wishes from friends and family and people I've never met before.

I would like people with Parkinson's to know, first and foremost, that there is hope. It may not come in the form of deep brain stimulation for them. It may come through other treatments. But, there is hope. This is not, by any stretch, necessarily a death sentence or even a life sentence. There is work being done every day to encourage people to live full and wholesome lives with movement disorders. [pensive electronic music fades out]

[upbeat electronic music] The team at the Krembil Brain Institute are doing a remarkable job and, you know, if I am an example of the work that they're doing, so be it. I'm impressed by my treatment and where I am right now. I know this may only give me another 10 to 15 years, but holy smokes, 10 to 15 years can be a lifetime, and to improve my quality of life as much as this has is a truly remarkable circumstance, and for that, I have to thank them. I can't say enough about the care and the quality of the treatment I received, and I just hope so many other people have the opportunity that I've had with the results that I've had. [upbeat electronic music continues then fades out]

Heather 11:59

[Your Complex Brain theme music] Joining us now to talk about the future of DBS and some of the more recent advances in research with this technology is Dr. Suneil Kalia, a neurosurgeon and senior scientist with the Krembil Brain Institute, and the Tasker Chair in Stereotactic and Functional Neurosurgery, and Dr. Alfonso Fasano, a neurologist and clinician investigator with the Krembil Brain Institute, who holds the Chair in Neuromodulation at UHN. [theme music continues then fades out]

Okay, so you two are probably the busiest people I know. I think it's a bit of a miracle that we were even able to coordinate your schedules to have you on the podcast today, so thank you so much for being here.

Dr. Kalia 12:50

Thank you, Heather. Our pleasure.

Dr. Fasano 12:52

Yeah, thank you.

Heather 12:53

Dr. Kalia, I know you've performed hundreds of these DBS surgeries, if not more, including Harry Forestell's. Can you tell us a little bit more about the procedure itself, and what's involved in a surgery as complex as this one?

Dr. Kalia 13:06

So, this is an operation where we have to balance a lot of technical goals and keep as safe as possible. There are many steps to the surgery. Basically, the ultimate goal of the surgery is to implant electrodes that are just over a millimetre in diameter to targets in the brain that are selected by the team that will give the best possible results for a patient, and these targets are quite small, in the range of five to seven millimetres deep in the brain. In terms of the operation itself, we do the surgery with a lot of advanced technology, and that technology includes imaging, such as specialized MRIs that allow us to have a map—a GPS map, if you will—of a patient's brain, and using that map, we define a safe entry point for our electrode, and we define a safe target and path down to that target.

We tailor the surgery to the needs of the patient, so we can do this operation with a patient relatively awake, and this allows for detailed testing and fine tuning of the position of the electrodes, or for certain patients, we can do this mostly asleep. It's a matter of balancing patient preference against the goals of the surgery. Throughout the surgery, we use other types of technology that allow us to further fine tune the position of the electrodes, and this includes, but isn't limited to, recording individual brain cells to identify the regions of the brain and further refine our target, and using three-dimensional imaging to see the position of the electrodes. That's part one of the surgery, and once that's complete, part two of the surgery involves connecting those two small electrodes that are deep in the brain to extension wires that run under the skin behind the ear, down to a computer that's implanted in the chest area. And, the total amount of surgical time varies, but part one takes about three to four hours to do, and part two is about one to two hours to complete.

Heather 15:17

That's amazing, I mean, just that you're able to determine exactly where to place the electrodes and which areas of the brain to target. Dr. Fasano, Harry obviously had a very positive outcome from the surgery, but how often is that the case? I mean, what is the success rate for DBS, overall?

Dr. Fasano 15:33

This is a question that we get all the time and it's not an easy question to answer, because this is not cancer surgery where you have a success rate in terms of, you know, being alive at a certain time after a few years or not, so it's difficult really to define success, and usually, my answer is that success rate is close to 100% if the right patient is identified and the electrode is placed in the right target, and the patient undergoes the right programming and the right medication adjustments. So, as you can tell, it's a very complex process and success rate is also difficult to define because every person comes with different goals. [delicate electronic music] For example, in the case of Harry, we've been talking a lot about the effect of DBS on speech, given his job, so he could have been much, much better looking at the overall picture, but if DBS, per se, was to cause speech problem, then it will be a big problem for him. And so, he would probably not call that successful, so that's why it's so difficult to identify success. It's so dependent on the patient's functions, needs. Overall, our goal is to improve their quality of life, and this is why we spend a lot of time discussing with them and their family what their expectations are. A well-known problem of this procedure is disappointment after surgery because, unfortunately, even though this is quite remarkable, it helps a lot of people, this is just a treatment. It's not a cure. And, unfortunately, a lot of people go to surgery, even when they say that they know that the disease won't

go away, but in the back of their mind, they think that this will be it. It will be the resolution of the problem, and unfortunately, we don't have anything like that, so that's why research is still very important to improve these conditions from really the bottom of the problem so that the real issue that is the degeneration going on in the brain. That's the short answer to your question, Heather.

Heather 17:27

[chuckles] Well, I guess the other part too, is that when somebody arrives at DBS surgery, they've already seen you and your team first, as a neurologist. They've often tried different options and medications long before, you know, they're considered for surgery. How do you even determine if someone is a good candidate for DBS?

Dr. Fasano 17:43

Yeah, this is an excellent question. Often, we rely on the referring neurologist's assessment. There are not many movement disorder specialists in the country, so I would say I know very well them all, and I don't have any reason to question if the right medications were used. In the best interest of the patient, we work as a network. We try to get as much information as possible in a short time, which is what we call the two-day assessment. We put a battery of tests that is meant to really give us an understanding of what's going on, and this includes neuropsychological testing to assess memory, attention, or the brain function, an important evaluation by the psychiatrist also to assess expectations, depression, psychiatric problems. Parkinson's is not just a motor disorder. We need to clarify that. And, we also do a Levodopa challenge and Levodopa challenge means that we see how Levodopa helps patients, because that helps us understand what type of target to choose, what type of prediction of improvement we can tell the patient. We also look at the brain anatomy with an MRI, and more importantly, we spent, I would say at least an hour discussing what they want from it, what their goal is. [delicate electronic music fades out] I truly believe that patients and their family are part of the team and, therefore, they have to share some responsibilities in deciding what's best for them. And eventually, it's a team decision. We have an additional meeting with Suneil, other colleagues of ours, all the people involved in this complex multidisciplinary process to finally say, "Okay, these are go. Is it DBS?" "Yes," because we also consider alternative treatments. It is for one side of the brain, for two sides of the brain, in this target and this other target, with this type of battery, with this type of electrode. And then, the timing.

Heather 19:20

Yeah, it's no easy decision, any which way. You mentioned Levodopa. We haven't actually talked about that yet, so I just wanted to ask if you can just explain to the audience, you know, what is Levodopa?

Dr. Fasano 19:30

Levodopa is the main drug used for Parkinson's disease. In a very simplistic way, in Parkinson's, there is lack of dopamine in the brain and Levodopa gets converted into dopamine in the brain, so it's like giving insulin to someone with diabetes, so you give them what they miss. There are, however, a few problems. Not all the signs of Parkinson's improve with Levodopa. A classic example is tremor. And also, over the years, Levodopa still remains effective, but the duration of effect can shorten, or Levodopa can be causing involuntary movements that we call dyskinesias. So, in other words, the brain wants something constant, not something that goes up and down in the bloodstream, like Levodopa does, and this is actually where deep brain stimulation has a role.

Heather 20:15

So, I've been really fortunate to actually be in the room with you with a patient, in the past, that first moment that you've actually turned on the device. It was pretty spectacular to see the patient's reaction

and some of the changes in some of the symptoms that they had been experiencing before. Tell me what it's like for you as a physician, that first moment that you turn on the device?

Dr. Fasano 20:36

Oh, wow. This question brings me a lot of memories because it's the reason why I decided to become a neurologist. I saw my first DBS patient when I was 20 years old. I was in an anatomy class in Rome, in Italy where I was trained, and someone came, because at this point, we know everything in theory, but we don't really understand why we need to know, for example, that we have a target in the brain called thalamus, so our professor brought to a class a patient who had just undergone this procedure. The patient was off, and the stimulation was turned on, simulating the thalamus, in this case, and the patient went from being Parkinsonian to be normal, and that was mind blowing. And, 25 years later, I'm doing what I saw in that room on a regular basis. The field has changed profoundly and it's actually nice. I think I'm in a privileged position because I have seen the evolution of the field and I can tell you that the more I do this, the more I realize that the real evolution here is the human relationship between the patient and the doctor. You know, you can talk about technology for hours and hours, all these fancy pictures that we see on the internet or publications, but what really makes a difference is that connection that you establish with the person that you turned on in that particular moment.

Heather 21:50

Dr. Kalia, I wanted to ask you, as well. I mean, your role is really focused on the OR and the surgery itself, but what is it like for you to see a positive result in a patient that you've operated on?

Dr. Kalia 22:00

For me, after having done this operation hundreds and hundreds of times with many patients that are awake, that moment that you turn on the stimulator and you see a tremor disappear, or someone's Parkinson's symptoms improve to a point that it was like five or 10 years ago in an instant, never grows tiring for me. And, similar to Alfonso, seeing those operations was the inspiration to enter in this area of neurosurgery and help advance the field. The seeds were planted early, when you could see the immediate difference that you can make in a patient's quality of life.

Dr. Fasano 22:43

Suneil is a special individual, and I will say I'm lucky enough that I work with a lot of neurosurgeons and, in particular, the team at the Western, Suneil being one of them. There is an ongoing discussion, not just about what to do next, but also how things are going in general, and this is really the key of being really part of a team that puts the patient and the family at the centre, but we work together, and this is one of the things that make Toronto Western, but in general, Canadian centres, the best because it's really an interest in helping and understanding at the same time, while in other countries, it's really a separate process. [rhythmic electronic music] The neurologist sees the patients before and after, and then your surgeon sees the patients only during the operation and that's it.

Dr. Kalia 23:28

I echo that because part of this is working as a team and combining the expertise of many team members to deliver the best care possible. I'm sure for a given patient going through a DBS journey, the amount of combined training that all the team members have that are looking after the patient, I'm sure would be, you know, 75 to 100 years' worth of training. I think it's amazing to take all these very high-level experts and speak a common language and work to improve someone's quality of life, and I derive a lot of satisfaction from that approach. [rhythmic electronic music fades out]

Heather 24:11

Can you speak a little bit more about the unique approach at Krembil Brain Institute in terms of some of the other team members who are involved?

Dr. Kalia 24:17

Sure. So, for deep brain stimulation, the journey for the patient starts with a neurologist, and then the patient will be referred on if that neurologist feels that they may be a candidate for deep brain stimulation. And, I know we're speaking on Parkinson's disease, but I just want to also highlight that the surgery is done for other types of movement disorders including essential tremor, dystonia, as well as epilepsy and very select cases of patients with severe types of pain. So, the journey starts with a neurologist and then is referred to the DBS team which, here, we have two neurologists. Dr. Fasano is one of them. Dr. Munhoz is the other, and they quarterback a much larger team that includes neuro-psychiatrists, neuro-psychologists, nurse practitioners, and then there's the neurosurgeons, and then we have additional team members during the surgery, including neurophysiologists that help us record and interpret recordings from the human brain. There's the anesthesia team, the nursing teams, and then the journey continues back to the neurology teams with Dr. Fasano and Dr. Munhoz, and as different issues creep up in the patient's journey, it may be that someone's mood is affected by the surgery or their reaction to the surgery, then that hub can then go along the spokes of a wheel, back to the experts on the matter and try and help the patient, either related to any issues that arise with the surgery or optimize the setting so they can derive the best result. But, we have to keep the expectations realistic, and so part of our job is to also temper expectations that might be beyond what the therapy can deliver in the first place, and temper expectations as to what may be coming down the road in the next five or 10 years. So, that's also part of our job, and sometimes that means delivering difficult news or difficult decisions with the patient and the patient's family.

Dr. Fasano 26:28

If I may say, there's another important parts of the team that doesn't receive enough credit, and these are... Well, there are two parts – the assistant, the staff that is in charge of booking, speaking to patients and families, and it requires a lot of effort. It's also coordination, as you can imagine, when you deal with so many team members. And also learners. We can probably do a quarter of what we do without international and national postdoc fellows who come from really everywhere to learn what we do. They are highly motivated neurologists in my case, but also neurosurgeons in the case of Suneil's team, and they come from everywhere to stay year to year, some of them with young kids. They move here with their own family, and they do it with the strong motivation of learning this technology and this treatment so that they can take the whole package with them when they go back home. And, in a way, this helps us tremendously, but also we give back to them and to the people and the patients that this fellow will eventually meet in their career. So, our reach really goes beyond Canada, and the beauty of an international program like the one we are working in, at each given time, we have between four and six fellows only in the DBS neurology part, just to give you an idea of the volume of these motivated neurologists. But so far, in the 10 years I've been in Toronto, I trained close to 40 neurologists on this technology.

Dr. Kalia 27:52

For our program, training the next generation, the people that are going to look after me and Alfonso in the future [Heather laughs] is absolutely critical, and it's very rewarding. It's like we're planting seeds, globally, of the leaders of tomorrow, and it's rewarding now watching those people that were our fellows now, leaders at meetings and starting to develop programs of their own in many parts of the world. So, it's actually quite exciting to see that.

Heather 28:21

Well, as long as you're not planning your retirement. [laughs] Dr. Kalia, you know, oftentimes when we speak about DBS, the term neuromodulation comes up quite a lot, and I think that term might be confusing to people who, you know, don't live in this world. So, can you explain – are the electrodes that you're implanting actually changing the circuitry of the brain?

Dr. Kalia 28:43

To me neuromodulation is anything that can change or adjust circuits within the brain with a goal of improving their function or restoring their function back towards normal, so shifting away from a disease state and resulting in improved quality of life. So, in terms of DBS, it's been around for a long time now, and the field is evolving, but it's one of these home runs that the field has had, for which the benefit was realized much before how it works was understood. [rhythmic electronic music] Substantial progress has been made as to how DBS might work, but there still remain significant mysteries. In a nutshell, depending on the disease that you're treating and the target, the mechanism of action of DBS may be quite different. What you're doing is you're applying electrical energy in a location in a brain, and you can look at it as the flow of information like traffic lights, and you may be turning some traffic lights that are now red, because of the disease, back to green, and the flow of information with these circuits then is reset or restored back towards a more normal state, and that manifests as symptoms that are improved. And, this can occur immediately. So, for example, in the case of central tremor, as you turn the device on and off, you can see the tremor disappear and reemerge, or it can occur over time, so there may be some type of plasticity that occurs in these dysfunctional circuits. [rhythmic electronic music fades out] So, that would be, for example, epilepsy or dystonia, where the benefits of stimulation can take weeks to months to manifest and, if you turn the stimulation off, it may actually take weeks for the benefits of the stimulation to disappear. So, it's quite remarkable that, even with the same technology, the same electrodes, that you can have very different effects on brain circuits depending on where the device is positioned, and how it's programmed by the neurologists and the neurology team. The number of settings and parameters that they can utilize for this purpose is infinite. Part of this and the evolution of the field is to understand how to find the best target, but then once you're there, how do you narrow down the infinite parameters that may help this patient to drive the most benefit in a practical manner?

Heather 31:19

Well, Dr. Kalia, I know you work, as you mentioned, with a lot of patients who are living with epilepsy and the goal of DBS there would be, I'm assuming, to help reduce their seizures. So, this is the part that really fascinates me is this whole idea of how do you identify where in the brain seizures are coming from?

Dr. Kalia 31:36

That's actually a very complicated question and there's an entire team and expertise in place for that at Krembil. So, a patient with seizures that are not well controlled on medications should be evaluated by an epilepsy team as we have at the Krembil, and that team will then do a series of tests including admitting a patient with epilepsy on the ward and studying their brain over a period of a few weeks, and if the seizure location cannot be identified, then the patient may be recommended for surgery, in which we—and by we I mean, myself and my colleague, Dr. Taufik Valiente—we together implant many electrodes—it can be in the range of eight to 15 electrodes deep in the brain—and in this case, unlike deep brain stimulation, these electrodes are listening to circuits in the brain and we can use that information to identify where the seizures are coming from, so it's a diagnostic surgical procedure. From

that, then the team convenes and then decides what's the best next operation, and those can fall into two categories, and so that can be resection or ablation, so meaning you remove, with open surgery or with laser, the area of the brain that is causing seizures, or neuromodulation, which would involve implanting a vagal nerve stimulator or a deep brain stimulator, and so that's the part that Alfonso and I work on together, as well, with the other epilepsy team members, again, this very collaborative approach to working to finding the right settings that may help a patient's seizures. So that's another example of neuromodulation, a group of patients with epilepsy and how that team works together as well.

Dr. Fasano 33:30

If I may add, we have been really interested in the brain stimulation for epilepsy. It's true Canada was one of the first countries in the world to approve this therapy for epilepsy, five, six years before the States, for example. And so, there's a lot more opportunities for patients. Again, this requires a multidisciplinary team and sometimes we'll even work with teams from the Sick Children Hospital, because this is another procedure that sometimes we do in kids. So, there are many more things, for sure.

Heather 33:57

Well, speaking of that, and sort of the advances in the technology related to epilepsy, I know that there's one technology that you're using that actually helps patients who receive this procedure monitor their seizures remotely. So, can you tell me a little bit about that?

Dr. Fasano 34:11

Yeah. Technology is in constant evolution. There are certain devices able to record the brain activity more reliably than just a brain diary, see what happens over the years in the brain of this patient. Yesterday with Suneil actually, we saw a patient and we could tell from the recording in the brain when this person was having a seizure, and it matched entirely what the mother had taken note of on her phone. That was actually quite nice to see that there was a complete match, and this helps because not always is the caregiver or parent or spouse able to keep track of what's happening, but also sometimes seizures are not necessarily being identified by the person, or they're happening in the middle of the night, so there are advantages to better monitoring of what happens and we are not able to do remote monitoring in order to access the brain activity that is recorded while the patient is at home. We need to have, anyways, the patient in with us.

The remote care portion comes with another type of device where we are able to program remotely using the internet, and this is important also to increase the opportunity to people who live far from our centre. Sometimes we say no, even in people coming from Ontario itself. Ontario is a big province, as we know, and some people are too far – simply too far for them to be receiving treatment in a safe manner, but because of remote programming, we can turn it off, we can adjust settings very easily. It's like a FaceTime call, basically. Because of this, now a lot of people are more interested and they can have access to this treatment, while in the past, it was simply too dangerous.

Heather 35:43

[delicate electronic music] Dr. Kalia, I just wanted to follow up on epilepsy for a moment. If you can monitor seizures remotely, is it possible that the technology could one day stop seizures as they're happening or even detect them before they start?

Dr. Kalia 35:55

Yeah, so versions of that technology are already available on label in the US. So, this type of technology is called closing the loop or closed loop stimulation. So, in general terms, what that is, is you sense some signal possibly from a wearable device, and then you adjust the stimulation accordingly. And so, your example with monitoring a patient's brain and then changing stimulation at the time of detection of seizures, is actually available on a device that's been available for some years in the US, not available in Canada, but some of the current devices that we use will have that capability in the future. That capability is available for research, so part of our job at a centre like ours is test these technologies. Do they have value for our patients? Newer and more complex doesn't automatically mean better or better results for the patient, and so these are things that we would like to study in the future, not just for epilepsy, but for Parkinson's tremor or other types of disorders of the brain is can we define signals that we can detect and respond to? [delicate electronic music fades out] And what that will do for our patients is the disease and the symptoms from the disease are not the same throughout the day, so to have responsive hyperstimulation that closes the loop will then give the patient the best symptom control throughout the day, even if the disease is fluctuating. So that's the concept of closing the loop, and that's something that we will see very soon in the clinic.

Heather 37:40

It's amazing. Dr. Kalia, you're also working on imaging work, looking at individual brain cells all the way up to imaging a whole brain. So, what is the goal of that research? What can it tell you?

Dr. Kalia 37:52

So that's not my research, specifically. We're a collaborative team, and that's one of the beauties of working at Krembil. We have imaging experts, and so we're looking at a few different things, and so one is, even though MRI images look beautiful when you see them, their spatial resolution—we call it—may not be accurate. So, if you see your brain target and it looks as it would in an anatomy textbook, but it doesn't appear geometrically in the right location, that can be a limitation for using that beautiful image for surgical planning. So, that's a scenario where what you see isn't what you get, and so working out paradigms to improve that type of imaging to make it accurate spatially, and we may end up doing that with using MRIs that are actually less powerful magnets, that allow for higher spatial accuracy and equally good images. So, that's one example – improving the images so they're useful for surgery and the more you can see accurately, will allow for safer planning.

Another example is can you use types of imaging with stimulation on and off to understand how the brain circuit is changing? And that may have implications in reducing programming time in the future. A third example is once the electrodes are in place, can we use the imaging to show exactly where they are? And then, when Alfonso and his team have a patient after surgery, they can potentially substantially reduce their programming time because they'll know exactly in that given patient, with that patient's own anatomy, know exactly the configuration of where the electrode is relative to the target, and possibly give them a starting point that's closer to what the patient needs and reduce the significant amount of labour that they have to put in at the beginning to test that infinite parameter space that I was referring to earlier. So, those are three examples of various teams that are looking at improving the surgery itself or improving the programming that comes after the surgery.

Heather 40:18

It's really incredible. For all this time in Parkinson's, and many of these other brain diseases, there really haven't been any disease modifying therapies, and so the focus has always been on treating the symptoms and improving the quality of life for these patients. Are you optimistic that some of the

advances—exciting advances that we've talked about today—will actually lead to better therapies for patients?

Dr. Fasano 40:40

First, obviously, research requires a lot of funding. For a long time, there's been too much interest in finding a cure, and not much in finding new treatment, and this is something that everybody wants initially, but then when they start having their problems—I'm talking about patients or their families—they start saying, "Oh, why do we still have Levodopa that's been around for 40 years or more?" and DBS is the same thing over and over. As a matter of fact, DBS has been around for three decades now. "Why don't we have new symptomatic treatment?" So, this search for the cure can backfire because we can forget for a second that we also need research to find symptomatic solution, think about balance disorder, memory problems, speech disorders, so there are many things, let alone all the research that is missing in rehabilitation sciences. Rehab is fundamental for these problems, and yet there is very few research. The turning point is recognizing that Parkinson's disease doesn't exist. We should call it Parkinson's syndrome, or we should use the plural of disease, because every person with Parkinson's has Parkinson's for a variety of different reasons, and sometimes more than one reason at the same time. There are some subsets of Parkinson's where we know what's happening at the molecular level, and this is precision medicine so identifying the reason, patient by patient, and intervening on that particular reason for that particular patient. So, the consequence of these approaches that we will have therapists—and I'm sure we will have very soon, actually—that are tailored to a specific group of people, so it won't be a one-size-fits-all, for sure. Some people even argue, "What's the difference between a symptomatic treatment that's so effective, that removes all the problems, and a cure?" At the end of the day, we're actually dealing with the same thing.

Heather 42:26

[driving electronic music] Dr. Kalia?

Dr. Kalia 42:27

Yeah, so I think Alfonso highlights exactly the challenge we have and the advocacy that's required in the field that, if we're in a scenario where, with limited funds, care versus cure is being pitted against each other, we need heavy investments in both for the reasons that Alfonso outlined. On the care side, neuromodulation can only do so much, and for each patient, we need to figure out ways to personalize therapy, and that could be at the molecular level. This has exactly been the challenge in the field for generations now is how do you cure a neurodegenerative disease or a condition in which brain cells are being lost? And this is an extremely challenging problem requiring a lot of expertise, and what I think will happen is that for a cure, the field will have what's called a disease modifying therapy. So, to slow the progression of a disease like Parkinson's would be a major milestone, so turning something from having a progression over a certain amount of time to having a progression over many decades, that the worst of Parkinson's may never come for a patient with the disease, and I have to say our patients have been very generous. Many of them want to work with us on the studies, understanding that it's not necessarily going to benefit them. It'll benefit the future patients with the disease, but we also want to see if there's ways to do this and strategies that are being employed by scientists at Krembil including our lab, include repurposing drugs, for example, so using ways to identify drugs that are known to be safe and seeing if they may have a benefit in something like Parkinson's disease. Repurposing technology, so as Alfonso mentioned, we've had DBS now for the better part of three decades. A lot of people may not be aware, but for patients with Parkinson's over the last two decades, gene therapy has been tried, injecting growth factors in the brain. Stem cells have been tried. So, these therapies, to date, have not resulted in a home run or a disease modifying therapy, but they've established safety. They've

been very important studies. So, in the future, are there ways that we can take and repurpose DBS to control gene therapy or regulate the biology of disease or deliver new growth factors and control them in the brain? So, that's the concept called molecular neuromodulation. These are all things that I think are within our grasp over the next decade but require substantial amounts of research. So, there are a lot of exciting things happening in the field, including new ways of delivering things into the brain safely without incisions, for example, using focus ultrasound. All of us wish we had more time and funding to investigate. We have all the expertise here to embark on these, and so it's clearly something that requires advocacy because we need excellent care for patients today and continue to develop and study the new technologies and treatments as they come out, but we also should, as teams, still work on that very difficult problem of disease modification. [driving electronic music fades out]

Heather 45:54

All right. It's all about the patients and patient outcomes. I really enjoyed our conversation today, and I'm sure our listeners did too, so I just want to thank you so much for taking the time to be here.

Dr. Fasano 46:04

Thank you.

Dr. Kalia 46:05

Thank you.

Harry Forestell 46:19

[gentle electronic music] The reality of my life is that I have lived for about 35 years telling stories of one sort and another. The fact that I'm at the centre of this story really is neither here nor there. It isn't about me. It's about the treatment and about the remarkable results that can come from it, and if that gives comfort and direction and hope to others, then my job is done. I mean, the benefit of me being at the centre of the story is that [chuckling lightly] I didn't have to chase around and find someone who was in this situation, because I'm right here. So, you know, I know the story is about me, but I tried to find a way of telling that story from a more scientific and clinical point of view, as well as from a personal point of view.

Heather 47:30

[Your Complex Brain theme music] Thank you to Dr. Suneil Kalia, Dr. Alfonso Fasano, and to Harry Forestell for joining me on the podcast today. If you'd like to hear more about Harry's Parkinson's diagnosis and his DBS journey, head to our website at uhn.ca/krembil, and make sure to click on the show notes for today's episode.

This episode of Your Complex Brain was produced by Jessica Schmidt. Our executive producer is Carly McPherson. Thanks also to Dr. Amy Ma, Twayne Pereira, Suzanne Weiss, and Megan Andheri for their production assistance. [theme music continues]

I hope you enjoyed today's episode, and if you did, I would love for you to tell your family and friends about Your Complex Brain, and don't forget to leave a review on your favourite podcast app. Thanks for listening. We'll be back in two weeks with another exciting episode. Have a great day. [Your Complex Brain theme music continues then fades out]