Marie: Hello and welcome to *The Parkinson's Research Podcast: New Discoveries in Neuroscience*. I'm your host, Dr. Marie McNeely, and I've partnered with The Michael J. Fox Foundation for Parkinson's Research to bring you to the forefront of the field of neuroscience to discuss the latest advances and discoveries with leading experts.

The Michael J. Fox Foundation created this podcast for researchers, clinicians, and industry professionals with the hope that these conversations and the resources that we share will advance your efforts and partnerships to improve brain health. We're welcoming guests with a range of experiences and viewpoints, and the views expressed belong to the guests themselves. Today, we are excited to welcome Dr. Michael Okun to the show. Listeners, Michael is co-founder and co-director of the Norman Fixel Institute for Neurological Diseases at the University of Florida, as well as medical advisor for the Parkinson's Foundation. He is a board-certified neurologist, movement disorder specialist, neuroscientist, author, and an expert on deep brain stimulation and neuromodulation for movement disorders. So, today we're excited to talk more about Michael's work and some of the recent advances in deep brain stimulation as well as other areas. So, Michael, welcome to our show today. How are you?

Michael: I'm terrific. It's great to be with you.

Marie: Well, we are so excited to have you with us, and we're looking forward to learning more about you and your work. And I know your research has covered a broad range of topics, but perhaps we'll start with deep brain stimulation and neuromodulation. So, can you talk a little bit more about, I guess, the current frontiers in research on deep brain stimulation and neuromodulation, whether it's for Parkinson's disease or other conditions that you've been investigating lately?

Michael: Sure. Well, for those of you that are listening that may not know what deep brain stimulation is, it's much like what it sounds. So, we actually put a straw or a tiny little pipe into the brain, and we push a little bit of electricity into the circuits that control things like tremor, and stiffness, and slowness. And we try to modulate those circuits. And what I've done for a living for many, many years now into my third decade is listening to cells in the brain and trying to understand the language that they're speaking. And by understanding that language, we have the ability to modulate. And that's where it gets its name, neuromodulation. And we can modulate, and we can change the way the different areas are talking to each other.

And by doing that, we can improve folks' symptoms. And over the years, I've been involved in a number of different studies, not only Parkinson's disease, and tremors, and stiffness, and slowness, but also in walking and in a disorder called dystonia. My lab has been working on Tourette for kids and adults for many,

many years. And we also have worked on neuropsychiatric disorders like obsessive-compulsive disorder. And so, the actual procedure allows us the ability to use the conversations in the brain to try to treat these different disorders. And there have been a lot of advances in the field, at least over the three decades I've been involved.

Marie: Absolutely, I think the research has come a long way, but I think there's still a lot of unanswered questions. So, I think particularly surrounding where precisely to insert the stimulators and apply stimulation, and how do you know if the stimulator is in the right place? So, can you talk a little bit more about your work in this area of really optimizing the targeting for deeper in stimulation surgery?

Michael: It's kind of like real estate in a way. We think about location, location, location. And many, many years ago, my mentor, Mahlon DeLong, who also worked with Peter Strick and Garry Alexander to describe a lot of these circuits in the brain. They actually used little viruses that could trace the different areas precisely where your arm is, precisely where your hand is, and look at all of those different areas and how they connected to the top of the brain called the cortex. And through these circuits, we began to understand, oh my gosh, there's actually what we call a somatotopic representation ("somato" meaning body). So, there's actually a representation down deep in these structures in the brain for very specific body parts and body regions.

The reason that's important is that millimeters matter. And so, when we map the brain, some people call me a brain mapper, we're actually trying to understand in three dimensions where all of these things live. And if we can understand that and understand the trajectory, so the angle with which we'll place a deep brain stimulation electrode, we can get it into an area that would be optimal. Now, some folks like to call this a "sweet spot". I don't think that's very scientific, but it is in the scientific literature.

But let's just say the spot in the brain that's going to allow us to optimally deliver electricity, so the least amount of electricity, to improve the symptoms without eliciting or causing a side effect like problems with seeing, or problems with your arm pulling, or problems with some sensation that doesn't belong in your hand or in your lip. And so, the location we often say is – as I live in Florida and work at the University of Florida – so, if you miss the location by a millimeter, it can be the distance between Florida and California. If you miss it by two millimeters, it might be Florida to Australia.

So, millimeters matter. And where we see a lot of failures over the years. And I think University of Florida became the center where people would send their deep brain stimulation failures after we published a paper in 2006 in a journal called *The Archives of Neurology*, which is now called *JAMA Neurology*. These

cases, half of them were accounted for by electrodes that were not in an optimal position. So, to answer your question, location is really everything in this business.

Marie: Absolutely. And I think this is a key part of your expertise there at the University of Florida – is the process of “installing”, if you will, these deep brain stimulators. So, you mentioned that you're listening to the language of the cells talking when you're doing this surgery for deep brain stimulation. How do you know if you're in the right place, and what advances have come down the pipeline in terms of figuring out where to put these stimulators in real time during surgery for a specific individual?

Michael: Well, when we started, I was really useful. I'm a neurologist by training. And so, I liked to be on what Dr. Kelly Foote is on neurosurgery, and he calls his side of the operation “the clean side”. You know, the sterile side where he's doing the operation, and my side “the dirty side”. I'm like the navigator, and he's the pilot. And when we work together, and we advance what's called a microelectrode, and the tip of that electrode is about the size of a hair. So, we measure that in micrometers. I mean, really tiny. It's the same measurement unit we would use to measure one of your red blood cells. The tip of it, platinum, iridium, or tungsten. It's so small. It's really hard to see with the naked eye.

And we creep up on these cells, and we listen to them. And as we go by and through structures in the brain, what we do is we listen to their language. And some people have made the association that this is like driving through countries in Europe. As you drive through different regions, they speak different languages, right? And as they speak different languages, you need a new passport. And then when you pass through border areas and they ask you for your passport, that even sounds different when you're in between two areas.

And so, creating that map in three dimensions (so, we can pass the microelectrode multiple times to create a three-dimensional map) is classical brain mapping. And folks make fun of me because when I started, I did this with graph paper, and colored pencils, and these acetate tablets that were representations of one or two people's brains that had been turned in when they were done. We call them autopsy brains, and they had been cut and sliced. And so I could see where the structures were and then try to advise the surgeon based on the graph paper, and all the colored pencils, and the mapping where we were in three dimensions after we passed the microelectrode multiple times.

What has changed now in the last 10 to 20 years is that we've gotten better and better. We've developed our own homegrown system. There are systems now that are available commercially as well. And these systems allow us to get much

better images. And so we've developed a scan sequence at the University of Florida.

It's actually kind of a joke. It's called the FGATIR. It's the name of the sequence F-G-A-T-I-R (Fast Gray Matter Acquisition T1 Inversion Recovery), and the letters stand for Florida Gator. So, it's funny when we hear people talking about the sequence because they say in Australia, they say the “F-Gateer”. And we're like, no, no, it's the “Florida Gator”. And the idea is that we've gotten better magnets. We've gotten better technology and better scan sequences. So, we can actually see the structures. So, when I first started with Kelly Foote, we couldn't see the structures in the brain. So, he really needed me to help to map these structures out because they were invisible.

Now they're visible and they've gotten much, much crisper. And then you take some of the young kids, like there's a young doctor that just graduated from our fellowship that is now at University of Florida named Josh Wong. His whole career is on AI and connectomics, and how these areas connect to each other and understanding that and layering that on top.

So, when we think about the language that we started with driving through Europe, we layer on top of that three-dimensional representation. We layer on the improvements in imaging. And then on top of that, you take a young kid like Josh Wong that does AI and is able to tell us how things connect and where all the pipes are. And now we're in business and we start to put all that information together, and we can create a much more accurate image, not only of where we are as we're putting the lead in, but also where we get to because sometimes we don't get exactly where we expect to be.

So, that has helped us. And we are also helped by so many folks being referred from all over the world. Every continent, except for Antarctica. We have a very busy clinic where we only deal with troubleshooting. People who have had difficulties with their DBS devices. So we've seen where people have made mistakes.

And I'll tell you, that's an advantage when you see a couple of those every week. We then understand and then we can try to articulate and write papers and help people to decrease that error rate and figure out why people are making errors and where they're making errors. And so, the field continues to evolve. And I think it's safer. And as we can do this by passing less probes through the brain, we cause less trauma, less chance for what are called hemorrhages, or bleeding, or strokes. And so, we're getting better and better at this brain mapping. But I will tell you one thing that I tell all the students. The old fashioned way I used to do it still works with scaled graph paper, colored pencils, and acetate tablets.

Marie: I love it! Well, it sounds like the technology has come a long way. And I know once you make that decision of where to put the electrodes, then there becomes a lot of questions related to programming. And I know there are some different types of stimulation that could be applied, “traditional deep brain stimulation for Parkinson's disease”, for example, for tremor or something like that.

And then there's some new protocols or new paradigms out there such as active recharge by biphasic DBS. And perhaps you can unpack that for us and talk a little bit about how you make these decisions about then what kind of stimulation or what parameters to use to deliver that stimulation.

Michael: So, there have been advances in the technology and how we deliver the stimulation to the brain. So, this is like a brain pacemaker. And the pacemaker is connected to a battery that's much like your iPhone. And we can change and update that app, if you want to call it an app, but we can update what's called the firmware. It's the same thing like updating an app on your iPhone and change the way we give the pulses. So we can, for example, change the shape of a pulse that's into the brain. We can change the length of a pulse. And it turns out in order to get really good results in Parkinson's disease, let's just take Parkinson's as an example. We need to provide more than 100 pulses, in most cases, per second. That's the number of hertz. Okay. 100 pulses. Think about that. How many seconds have just gone by with me talking? 100 per second.

And then we can change how big those pulses are in microseconds. And as we have learned to program these devices, and the devices have gotten more complicated and have gotten more little contacts that we can program, it turns out that there are tens of thousands of combinations. And it's become very complicated for people to be able to program the devices. And that's where AI and that's where computer technologies are beginning to enter the realm to make this even feasible for folks to be able to offer stimulation. Now, these days, we're able to change the way that we give the pulses. And so in our laboratory, instead of giving a pulse and having it rest, we can do what's called biphasic stimulation. And so, that's something that you've mentioned and we've done a number of studies on changing the waves and the shapes. So, biphasic is a way to change the shape of the stimulation. We can also shape the stimulation in a different way by using technologies that have what are called independent current sources. So, imagine you have a piece of fruit. If one of the contacts gives you an apple, and another gives you a pear, and one gives you a lime, you can light up these different spots on the electrode with different sizes and different shapes out of different little contacts that spread the electricity out. So, we can actually shape it into a very complex object. So, that's one strategy.

Another strategy that we have that we didn't have three decades ago is, you can split each one of the tiny little contacts that push the electricity into three. They

call those segmented. And then you can steer the current. So, let's say the electrode was put in a little too close to an area of the brain that causes motor pulling when you turn it on. You could turn one of those segments of the lead off that's closest to that area and perhaps be able to push enough current through the other two to get the effect that you want without causing the side effects.

And so that's called segmented leads. And so, there are now a whole bunch of different things that we can do to actually program the device and to individualize therapy. Now, the name of the game at the end of the day is trying to figure out a way to turn that stimulator on to give the maximal amount of benefit with minimal to no side effects. And hopefully to do that with the least amount of electricity that you need. So either the battery lasts a long time or you don't have to keep recharging yourself.

So, these are the challenges that face us. And one of the biggest challenges, and we just completed a very large National Institutes of Health R01 with Christopher Butson looking at access and nurses being able to program these with tablets and other technologies that have been developed here and at other places. If we don't figure out a way to make this simpler for folks out in practice, we're never going to get the penetration. We're never going to get these devices out to all of these people that we know they can help.

And so, this has been a big challenge is that we're developing all these technologies that are awesome. And everybody's like, this is just tremendous. At the same time that we're doing that, we're making it so complicated that we're reducing access. And s,o this is the balancing act. And this is going to be one of the things that we're going to be most challenged on is the logistics, the FedEx, the UPS. How do we deliver these technologies, not just invent them?

Marie: Absolutely. And I'd love to dig into some of these details of the study that you referenced. This MAP DBS, we'll call it, mobile application that helps with programming, because I think this is a huge challenge, as you alluded to. In these programming sessions, if you change one thing, sometimes some things get better and some things get worse. So, in terms of making a decision of what is the optimal programming, it can be hard to figure out what to do next. So, can you talk a little bit more about this?

Michael: Yeah. So, as we think through this idea that, okay, you've got tens of thousands, if not more, possibilities of how you can turn this device on. In your general doc, at the emergency room, there's a shortage of neurologists. How in the world are people even going to have the time to go through all of these things to program them? And there's been this notion, a little bit of elitism, if you will, from people like me. Where you're like, well, you need somebody really smart to do this. So, one of the tenets, one of the things that we really wanted to lay out, was that it

was possible to create technologies that could bridge that gap. And so, what we showed in the MAP DBS study with Chris Butson was that we were able to develop a tablet that could be placed in the hands of an expert nurse programmer in the clinic setting and help them to program the device. And to do it potentially faster. And then put it in non-experts, and have them travel out to people's homes and do it in their homes. And we showed that the non-experts could do just as well as the experts. So, that's good news, right? That's great news.

And now since COVID-19 and all of the telemedicine advances, being able to adjust devices remotely is another thing. And bringing care into people's homes with diseases like Parkinson's, particularly those with mobility and other issues to access, is going to be important. And so, that idea of showing that we can actually take it out of an expert's hands is really important. We know that sounds a little bit crazy, but taking it out of the expert's hands actually makes it more accessible to people. And if you can do that safely and you can provide a means to get these technologies out, then they can penetrate and they can actually help and impact more lives. And so, we think about, as scientists, that we do all this work for all these years. But if we can't actually get things out to impact people's lives, and do it at a scale that can really make a difference, then in some respects we failed. And so, we have to pay attention to these things. And that's why I think this MAP DBS National Institutes of Health Study, and other studies like it, are really important. How are we going to move this technology into the home and out of the experts' hands?

Marie: Absolutely. And I think a big part of the challenge surrounding developing this application is understanding how to systematize what an expert does or knows so that it can be done by someone who's not an expert. So, when you think about – maybe we'll stay focused specifically on Parkinson's disease – for example, now that you're exploring these different ways that you can change, whether it's the shape, the length, the frequency of the pulse, how do you know where to start so that you can start making decisions from there in terms of programming?

Michael: What might surprise you is just how much empiricism – that means trial and error – it takes to figure this out. However, over time, we've begun to develop wisdom from multiple attempts, multiple successes, and multiple failures over many, many thousands of folks who have had the device to figure out what may work faster and be more reasonable. And if you can take the picture, now remember I told you we had the way that the brain cells talk to each other, the brain map. And then we have the picture, the MRI, or the CT scan, or both that can be fused together, and the connectomics. So, if you can take that picture, after the operation, you can tell where that lead is.

What we did in that MAP DBS study was we were able to understand where those electrodes were, and that constrains. When I say constrains, meaning we can reduce the number of possibilities that a programmer needs to focus on. And we can even use AI to try to tell them what to set the device at. And so, the idea that once we understand the location in three dimensions better, once we understand where side effects might live, we might be able to actually go faster to settings that are optimal for individuals. Now, that doesn't mean that will be the perfect setting. It doesn't mean it will work for everyone. But let's say you get 90 or 95% of people set in this way. It makes it much more scalable.

And then you deal with the people where the electrodes, a few of them are a millimeter off in this direction or that direction, or there's a complication here or there, or they need expert programming at a university center by some self-proclaimed or a trained expert in the area. And that's fine. We would encourage that. But I think we have to figure out how to use these technologies in order to scale down those numbers to constrain where we should stimulate and how we should stimulate. And by feeding forward that information before you even start, it can be a very powerful thing. It doesn't mean you can't go back and stimulate in these other areas in different ways later, but it will reduce the burden for an individual who's implanted with this type of technology.

Marie: Absolutely. And I know, Michael, you mentioned that the goal is to optimize improvements while minimizing some of these unwanted side effects. And I know some of the unwanted side effects for deep brain stimulation include some non-motor changes. I know a lot of people think about sort of the tremor, the motor things that you can see. But with DBS, you get things like potential changes of mood, personality, agency, identity. Can you talk a little bit more about the state of the evidence regarding the impacts of DBS on these things, and through what mechanisms they might be occurring?

Michael: Yeah, I think for your listeners, it's really important to just appreciate what we're doing here. We're putting kind of a straw into the brain and pushing electricity into the world's most elegant, vast supercomputer. Right? There'lll never be one better than the human brain. I know that's hard for people to digest who are building all these great things, but we really have an amazing computer system that all of us run on. And when you have something like that, it is so complex, and everything is packed together. And you think about all of the super highways. If you have ever been to a big city like Atlanta, Georgia? There's a place called Spaghetti Junction where all the roads cross over each other. If you've been to LA and you see the big concrete of all the different pathways, that is just a small fraction of what it's like within your brain.

So, when you consider that all of these roads are so close to each other, and you push some electricity in. When we explain to folks who receive this therapy, there

is a possibility that we're going to push some electricity and drive a circuit that we don't want. It could make you happier. If it makes you too happy, like we've seen in some of our folks, you might be preaching off of your rooftop, which might not be the safest thing in the world for you to be climbing up on a roof and preaching to your neighbors. Right? But you might become manic. Right? If you hit a spot that makes you too euphoric, too happy.

Conversely, another spot might make you depressed, or anxious, or suicidal. So, when we think about these disorders, one of the great advances that folks don't think about a lot is over the years, when we first started doing this, there were a lot more suicides or a lot more cases of hypomania. Those of us that have been around a long time have seen how those circuits can drive impulse control disorders, shopping, buying things inappropriately, that can be driven if that current gets into the wrong space, or people can become very depressed. And those of us who have been around a long time know that as we were trying to figure the technology out, you end up with more of these side effects.

And of course, like anything, it evolves over time. And hopefully you learn to keep the electricity out of those circuits as much as possible. But as you're programming folks, and they say, I just need a little more tremor benefit, I just need a little more stiffness benefit, I just need to do this just a little bit better. A little bit better is like a dollop when you're cooking and a little extra dollop may put too much spice in there. And that may be enough to push them into one of these side effects.

And so we've become really good at monitoring. And folks don't even realize how good they've become at this. But because of these experiences, these formative experiences over the decades, we've become much better about asking questions and monitoring. And people say, well, we'd like to be able to program that device and set it and forget it. Well, I would say those of us that have been around a while will tell you that probably the more important thing in deep brain stimulation therapy isn't necessarily setting the device correctly, it's monitoring the person to make sure they're not getting apathy, or depression, or suicidality, or another effect, or they're too happy. Or they're playing golf all the time, which they might love, but it might be ruining their marriage. And so, it's important that we see folks and we're monitoring because we can inadvertently push electricity into the circuits. And sometimes when we're trying to get it just a little bit better, we can push over the cliff, and they can end up with something that can be a very meaningful change positively in one way, but also can be destructive in their lives in another.

We have to watch that balance. I like to remind people we have to still practice medicine. This isn't just about modulating the brain, this is about watching the

person with the disease. And the person, by the way, is progressing with their disease over time. And so, it becomes really tricky.

Marie: Absolutely. I think considering, as you alluded to, kind of the whole picture, the whole person is really important. And the progressive component was another thing that I did want to come back to. In terms of these programming questions we've been asking, we've sort of been talking about it from an initial programming angle. But as you correctly identified their disease is, for Parkinson's specifically, progressive. So how do you, I guess, take into consideration this changing landscape of the brain, within the disease of Parkinson's disease, when thinking about how you're monitoring or how you're sort of managing deep brain stimulation programming?

Michael: It's maybe the most important question in the podcast because in order to even move forward with thinking about somebody for an operation, we do what's called a multi-disciplinary evaluation. And I know that we coined a term called fast track, and it's not necessarily fast, but that's what we called it in the day. And it kind of stuck around the United States and around many regions around the world. And the idea was you would have a lot of different disciplines evaluate the person for deep brain stimulation therapy. And I often say, what's the best possible healthcare that you can wish for, and hope for, and get in the American healthcare system? That's when a whole bunch of people see you and then talk behind your back. So, that's not always true and other things.

So, you've got a bunch of people that see you talk behind your back. That's a multi-disciplinary or interdisciplinary evaluation if they're seeing you in real time. And having all of these folks evaluate you at baseline is important not only for determining whether or not you might be a candidate for an operation, but it determines your risk and your future risk and then how they want to do it. And so any center that is doing fast food, deep brain stimulation usually goes out of business pretty quickly because it's a pretty complex art. It's not like taking a gallbladder out and pre-opping somebody.

You're going to want to know where their entire cognitive function is and test all the different lobes of the brain. All their different memory and abilities, and how can they inhibit things? How do they initiate behaviors? All of those things have to be tested. Their response to dopamine has to be tested and how they perform on various motor tests. The neurosurgeon has to look at them. Can they tolerate a one-sided DBS, two-sided DBS? Which target, there are multiple targets in the brain, might be useful and might be safest given their age, given their other cognition.

And then we have occupational therapists that look at the sides, and look at their activities of daily living, look at what their expectations are for the surgery.

Physical therapists. Speech therapists to make sure if there's a swallowing issue, we watch that. So, once we've entered you into the program, we're watching you, and then if we implant you, however we decide to do it, one lead, two leads, and one surgical sitting and multiple, because maybe you have a cognitive risk and we need to go a little slower. Maybe we choose a different target because of that. Maybe you have too much dyskinesia. and you get one target or you want medication reduction, you get another target.

Over time, regardless of who you are, you're going to progress. And we're going to need to compare that to your baseline. We need to understand how you're going to progress. And guess what? The hardware is going to stay the same size, the DBS lead and the hardware, but your brain's going to get smaller. So, here's the good news, bad news for your listeners. The good news is all of our brains get smaller. And if we hit our heads and they swell up, when they get smaller, there's room (like in the Tupperware container) for the brain to expand as we get older. So, it actually can be somewhat protective.

The bad news is the brain gets a little smaller (we call that atrophy) a little faster with Parkinson's disease. And when we put a DBS lead in, we're putting it into a structure that's tiny. If we choose the subthalamic nucleus, it's 150 cubic millimeters. It's the size of a squished pea. If we choose the globus pallidus, internus, it's maybe three squished peas, 450 cubic millimeters. These are tiny, tiny structures. And they're getting smaller over time. So, that can change where the electricity is going on the superhighways. So, we have to pay attention to that as they progress.

And then they might develop features that don't respond to DBS, or they might not have those features on the front end. And they come in and they say, I want to walk better. Well, if I didn't walk well, I would want to walk better too. But most of the time, DBS isn't the best operation to help people to walk better. It can help sometimes with freezing and things. We have to have those formative discussions. And then as they emerge, people say, hey, change my setting, fix that for me, doctor. So we have to have gone over that with multiple people in a multidisciplinary setting. So they understand where are our limitations?

Now, our hope isn't that long term, we're going to be limited by all of these things. But we need to be very honest with people and to track them. And to have them understand once we get to some good settings where they're getting good benefit – here's a big secret from DBS – the majority of people are going to stick with those settings long term. Or very close to those settings. And the management is going to be multidisciplinary. Social workers, physical therapists, occupational therapists, speech therapists, watching medication timing, watching the types of medicine, seeing if we have emergence of memory issues that we

need to deal with or psychosis, or punding, or whatever the challenge is going to be.

We have to see these folks to meet that challenge. And so, I think there is a lot of light switch mentality. You're going to get the light switch, it's going to stop the progression, you're just going to keep going. But it is, as you said, it's a progressive disease. We need to pay attention. And if anything, if you're in the surgical area, you need to be really good at managing folks medically and on interdisciplinary therapies and rehabilitation therapies. B ecause they're going to progress and you're going to follow them through the lifetime of their disease.

Marie: Absolutely. And I think, Michael, you made a really important point there that a lot of people think of DBS as sort of a silver bullet, but it's not. There will always be limitations, things that you will not necessarily be able to address or address well enough with deep brain stimulation.

But I'm curious what your thoughts are on this at the moment. Do you think we're at a point where, with deep brain stimulator surgery, considerations about lead placement, stimulation parameters – do you think we're at a point where most people are able to be “optimized” to a point where they're getting good benefits without some of these side effects?

Michael: I think the question that you're asking is, are we beginning to scale the therapy? Are we beginning to get it out there? And people are getting the benefits that they hoped for when they received the DBS devices.

The answer is tricky. In the early days, there was this notion that companies could just give headframes out to everybody, and they could just learn how to do it. We could even rent a person to go into the operating room and help you to put the devices in and all of those things. So, there was this notion that anybody could do it because we saw these videos. Right? You see them online, particularly with social media, off DBS, on DBS. You're like, okay, I want that, sign me up. But that's not how it works for most people. And so, a lot of institutions, a lot of hospitals thought, sign me up for that bandwagon. And so, the ones that are left after they've been doing it for a while, who develop good multidisciplinary teams, that select reasonable candidates, follow them, take care of their progression, have programmers available, and are really thoughtful, even if they miss.

And every expert center misses. So, if you talk to somebody, and they say, “I never miss and I'm accurate,” or whatever, they're fibbing. I've been around this business a long time. I've seen a lot of misses. We all miss. The areas we're dealing with are too small. And if you miss, you’ve got to fix it. And sometimes we’ve got to fix it. And you’ve got to be honest with people. And so, I think the

centers that have longevity, that have been doing it for a long time, that aren't in it just to maybe turn a buck, really care about their folks, that have good multidisciplinary teams, that are selecting them well. And then after they implant, they're really thoughtful. They take a picture and they look, let's see, did, I get the lead where I wanted to? Is it programming the way it should be? Am I communicating back? Can we fix it? Can we optimize it? How can we work together?

Those are the centers that tend to stick around. And then there's what my grandmother would call the fly by night places. They come in and they come out to make a buck. So, I think as folks get into this, the experience matters. The people that have thoughtful teams are doing better and better. And we're seeing better and better results, but we still see folks that are not fully committed, that don't have the right teams, that aren't really having good quality programs, and they're not doing quality assurance. And one of the ways to get better at something is to just admit you're not perfect. Every day I practice medicine is humbling. I know a little bit less every day I practice medicine. And so, you're going to miss, you're going to be suboptimal. But if you send that information around, you get post op scans, your teams looking at every single case before, during, after, and everything is like a beta test, then every time you do it, you're going to get better.

So, it really depends. Your question is a great question, but it really depends on teams that are really willing to come to the table and want to keep getting better and put the right players out on the field. And imagine if you tried to field a baseball team with half of the players. You know? I mean, you can imagine what the long-term consequences of that is going to be.

That team's not going to be around for a long time, and their record's not going to be really good because they're playing with half the players, they should. And so, if they can get the right players to the table, and they have a commitment long-term, they care about people, then they're going to get good outcomes. And we're seeing better and better outcomes from groups that are able to do that. Absolutely.

Marie: That's really promising. And I know, Michael, you have decades of experience in this area, but what have been maybe some of the biggest surprises or maybe unexpected outcomes that you've encountered in your research?

Michael: We have seen some really interesting, fascinating, and just life-changing moments in the operating room and operating on different targets in the brain. There are oftentimes in this business a lot of serendipitous things that happen. And so, we operated on one patient and we were in the reward center of the brain, and we saw that they smiled on one side of their face and got euphoric and

then converted to a smile on the other. So, that was a stimulation-induced smile that's now been replicated across all the continents and is one of the features for obsessive-compulsive disorder DBS that you can use to predict outcomes. We've been able to see areas of the brain that can stimulate panic attacks, cause people to get depressed, cause people to cry or laugh when they're not happy or sad. So, we learned from these experiences.

Recently, in the Alzheimer's disease cohort we were operating on, it was a negative study, meaning it didn't meet its primary outcome goal, but we published a paper in *The New England Journal* because we saw in 30-40% of folks when we turned the stimulator on next to this memory center called the fornix that they would get these memory flashbacks. And as you turned up the current higher, it would like go from black and white to color. And so, we wrote about this. And so, the brain, and these connections, and what people call the connectome, and the circuits that we're driving are so interesting. It's so fascinating. And we just learn so much every day.

And so, over all of the years, all of the different discoveries, and let's say observations, you're never the first person to see it. You might think you're the first person to see it, one of my mentors used to say, but you're probably not the first and probably you've seen it before and never appreciated it. But as we've appreciated some of these findings in neuromodulation, it's been formative. It's been interesting. It's been fascinating. And it allows us to peek into the brain and think, how can we develop different therapeutics and different strategies to try to improve these symptoms? And one of the strategies that we've been working on for a couple of decades is taking those brain signals that we record and using them as biomarkers and teaching devices to respond to them. And so, we have an NIH Brain Initiative project with Aysegul Gunduz and Kelly Foote suppressing tremor. So, when you move your hand, it turns on automatically and suppresses the tremor. It’s really cool.

In my lab, we've been doing Tourette for many years. We have a device that can suppress tics and detect the tics. We have been involved in studies for Parkinson’s disease and making these devices smaller, sleeker, smarter is great. And it's not clear that we'll need all of that technology to solve the problem, but we're learning so much about what these signals mean, how they operate. And this information can be used not just in neuromodulation, but it can be used across many diseases and many therapies. And the more we understand the human brain, the better. And I'll just add, in my experience when I was in training, we did some work with monkeys and primates and things like that. But my laboratory now is the human operating room. It's awesome. And in the clinic, we're learning on the actual creature that is receiving these types of therapies. And so, it's kind of a real time adventure. And for Dr. Foote, and Dr. Gunduz, and Dr. Wong, and Dr. Ramirez-Zamora, all the people that are here on this great

team, for us, it's great because we have the opportunity to translate almost in real time. And that's pretty cool.

Marie: Definitely. I think the tools, the technology, the resources, and the research have really come a long way. So, Michael, when you think about the big picture and all of these advances, are there things that really come to the top of your mind that are really moving the field forward, whether they're from The Michael J. Fox Foundation or others?

Michael: The technology on the imaging side is really changing quickly and positively. From not being able to see anything, and you've got to bring in somebody like me to map it out with colored pencils, to where we are now. And then how much we can see, even without recording out of the brain, is pretty darn amazing. And it's only getting better.

We're going to see technologies here ('ve already seen a few) where they'll be able to even get to almost histological level. That's like, when you would cut a slide after somebody dies. Now, of course, we never take anybody's brain until they're done with it. But imagine if you could begin to start to do that and people who are alive and become very exact about where you're going to put electrodes.

There are a number of different studies that are going on now, looking at stimulating from outside the brain. And I'm not talking about magnets on top of the brain like transcranial magnetic stimulation, but Ed Boyden and colleagues at MIT, they invented a really cool technique, called temporal interference, where they can get deep in the brain by crossing the stream. So, if you've seen the movie *Ghostbusters*, they say don't cross the streams because something bad is going to happen when they're trying to extinguish the ghost. But in this type of procedure, when you actually push in these sound waves, if you cross them, you get the difference in their frequency, how fast they are. And you can stimulate deeper. And it doesn't look like you're disrupting tissue in between the two.

So, we've not had that idea that we could get deeper with these types of technologies that are less invasive. So, could we do this less invasively? It's having trouble translating into humans, but it's early days. And then people are using the technologies to upregulate little tiny particles called nanoparticles to try to only stimulate certain types of cells and inhibit other types of cells, so fiber-specific and cell-specific. And they're using magnets, and thermal electricity, and ultrasound.

And it's just, it's really cool. But the name of the game at the end of the day is understanding the circuits. Can we understand the biology of the circuits? And can we understand the disease? And then can we in some rational way apply all of this technology for the betterment of the person. Not for the betterment of a

researcher like me that wants to publish another paper or thinks it's really cool. Can we do something that's going to impact people, scale out there, get to a lot of people, have it be affordable, and really change how people are doing with Parkinson's?

And I think it's very fair to say that after dopamine, which was the first miracle in Parkinson's disease. We don't like to say "miracles" in medicine, but dopamine therapy was as darn close as you can get to seeing a miraculous change in people. The next big change was with deep brain stimulation. And that was really another just major breakthrough for folks. And how we're going to scale these therapies, make them better, make them more available, make them available for other symptoms that we're not able to treat really well, like the walking symptom we talked about, talking, thinking, and memory, I think we'll get there. But understanding those circuits is going to be really important. And so, we don't want to put a cart before a horse. And we want to make sure that we have really explored and put together our information so that we can be thoughtful as to how we can apply what is almost a playground, a sandbox of so many cool things that we can apply to the brain. So we can do it with some modicum of safety and with all good intentions to improve these folks' lives.

Marie: Oh, that makes sense, Michael. And I know you're specifically part of a group working on a tool called the BRAVO platform, which is a deep brain stimulation platform. It's the Brain Recording Analysis and Visualization Online (BRAVO), so, it's an open source visualization tool. Can you just briefly tell our listeners a little bit more about this tool?

Michael: So, this is a tool that was developed by Dr. Jackson Caglel and Dr. Cora de Hemptinne here at the University of Florida. And the idea is that as you're trying to deal with these devices, you have just tons of information streaming in. So, now you imagine you turn on these devices like an EKG. Now, imagine you had an EKG coming out of your brain at all times, pushing all this information forward, and you have to process this information in real time and actually see it in a way that you can make a decision and do something with that. That is actually not easy. And one of the reasons it's not easy is because you just assume, like your listeners are sitting here going, well, of course you would not. There's just more data. Like if you downloaded your brain, there's just so much data. And how to deal with it?

And then the other thing is that you have all these companies, and it's not a bad thing, competing for market share and market space. We love it. But what these folks wanted to do at UF was to provide some what are called open source tools. So, there's another one in the operating room that another group here developed called FROST. And this one's called BRAVO.

This is how you make it. This is how you can do it yourself in your garage, and it'll speed along. And it's so important because if you can solve a problem or the next logical question along the road, you're going to help everybody else to speed along. And I was just telling a group of students here today, I love reading the literature, and I love it when I see somebody publish something, and it moves the field forward, even if our group didn't do it. Because then I say, all right, let's move on. They did it. Let's go on. Now we know what the answer is there, or we're close to that answer. And let's move on to the next thing.

That's the way we all need to be thinking about how we can work together. And so, creating open source tools, congratulations to Jackson Cagle and to Cora de Hemptinne. They also won one of the Innovators of the Year awards here at the Innovation Hub at University of Florida, which is one of the top three or four in the country. So, I'm super proud of them, but even more proud of the idea of making things open source, so it can drive the field in a positive way.

Marie: Absolutely. And then just to tie in The Michael J. Fox Foundation here, Michael, do you have examples of how your own work has benefited from some of the tools and resources from MJFF, or perhaps collaborations, or maybe just this connection with the Foundation?

Michael: Ancient history for me, I had one of the very first Michael J. Fox grants many, many years ago. And investigators here at the University of Florida have had a lot of grants, collaborations, sat on a lot of committees. This is a great organization. And they've done a number of things in the neuromodulation space over the years. And a number of us have operated in that space and done some pretty, what I think is pretty cool, interesting, and informative work. We worked with them on projects to better understand the gait pathways and how to help people with walking and freezing. In areas of the brain, there's an area called the PPN.

Cora de Hemptinne here has worked on modulation in some of these non-motor circuits. And you mentioned those earlier for impulsivity, and depression, and anxiety. And recording out of areas of the brain that we typically aren't recording out of, that we need to understand what's going on in those different regions of the brain. They've been really great on the development of technologies. Cora de Hemptinne used to work with Phil Starr at the University of California in San Francisco. And they really pioneered a lot of the early technology in *Nature Neuroscience* and several papers looking at how you can put strips and larger recording fields over cerebral cortex up on the top of the brain while you're stimulating from some of these structures. And that work really led to the epiphany of how the mechanisms and how the orchestra is performing in Parkinson’s.

And one great example of what the work influences, it's very influential in the field. Cora de Hemptinne here had a paper looking at how the symphony performs. And when she stimulated deep in the brain in an area called the subthalamic nucleus and recorded up in the cortex, guess what happened to the symphony? The two desynchronized. The symphony became desynchronized. Now, when I do the same experiment in my lab for Tourette syndrome, when we capture tics, it synchronizes. So, there's a certain pattern, there's a certain queuing to these diseases and understanding the physiology, understanding the different circuits, and then going after some of the more difficult things.

And so Michael J. Fox has been willing to support investigators, us and many others, to go after some of the more difficult to treat symptoms that are really disabling for people and understand could we apply modulation therapies? So it's been great. And I think they've been terrific in the bioengineering space and terrific in just being open minded to think out of the box. I mean, look, if we had the answers, then we'd be done, right? We wouldn't be talking. And like my wife says every night, have you finished that Parkinson's disease thing? Because I think you need to move on and help with other diseases. And we're not there yet. So, we're going to have to start thinking out of the box. And I would say the strength of the Fox Foundation in my mind has been the willingness to go where others are not. And that's going to really help us to develop better therapies.

Marie: Certainly. And I think Michael, that was a perfect transition in terms of talking about how we sort of answer this question and solve the problem of Parkinson's disease. I know we mentioned in our introduction, of course, that you're an author, and we don't just mean scientific papers, but you along with Ray Dorsey, Todd Sherer, Bastiaan Bloem have authored a book titled *Ending Parkinson's Disease: A Prescription for Action*. So, can you tell us a little bit more about the book and maybe just in general, how your work is bringing us closer to finding a cure for Parkinson's?

Michael: First of all, these authors that you mentioned, including Todd Sherer, he and I were at Emory together at the same time many years ago. And this work was really interesting in that we really wanted to understand what it takes to end a disease. So, we spent several years doing a lot of research, trying to understand diseases.

But as it turns out, if you study how to end a disease, so if you study polio, HIV, breast cancer, and how people are doing it, we came up with an idea after looking at all of these different groups that the formula for this is what we call a PACT.

And each letter stands for something. So, P in PACT stands for prevent. You have to prevent diseases. You have to advocate, that's the A. A really solid

advocacy base to really move the needle. C stands for care. You have a disease that is now being diagnosed. It used to be every nine minutes. And now I'm told it's every six minutes according to the new epidemiologic information. And so, every six minutes, a new case. And now it's growing faster than Alzheimer's. It's actually the fastest growing neurological disorder, not just neurodegenerative disorder. Blow your mind, neurological disorder. We got to care for these people. If we don't care for them, Medicare is going to get bankrupt here, and other health systems are going to swallow under this. So, we have to begin to think about caring for people and reducing the economic burdens and other burdens on society as well. It's huge. And then the T is treatment and developing new treatments.

And I think where the authors of this book, where we're trying to move the needle is across all areas. For example, Ray Dorsey is just absolutely just the best person in the world at advocating on the prevent side for the P and understanding environment and environmental toxins, and how we need to ban paraquat, and TCE, and all the potentially preventable causes of Parkinson's disease.

The advocacy: The Michael J. Fox Foundation, we had an author Todd Sherer on with us on the book, and creating a group of advocates can move the world. And so the book, one of the things we're most proud of is it spun out this group of advocates called the PD Avengers led by Larry Gifford. And thoughts and prayers with Larry today. He's actually getting a deep brain stimulation procedure implanted today. And so, he's the leader of that group, and it's thousands and thousands of people strong.

We need a grassroots organization, as well as a celebrity presence. It's not just celebrities. It's Main Street that we're going to need people from all countries to unite, and it united around this book. And so, we were really proud to start to move advocacy in a larger and potentially bigger direction. And then of course, there's a bill in front of Congress right now with the same name as our book, the *Ending Parkinson's Disease* Bill.

And Ted Thompson at The Michael J. Fox Foundation leads a great coalition of organizations pushing for that, has bipartisan support. And so, hopefully that will move and change things. And I think other areas where we're making a huge difference is we've been working really hard with organizations like the Parkinson's Foundation to create centers of excellence, teach people how to model care, teach people about multidisciplinary care and multidisciplinary teams, save people in hospital. We have hospitalization kits that you can take and can really save your life and improve the care that you get within the hospital. So, there are so many things that we need to do to help folks to stay in their homes and to bring care to the homes with telemedicine.

And when we took our red card campaign to the White House, that was one of the things that we said. We need to expand – this COVID-19 thing ended for telemedicine across the states. And now we're back to where we were before where if you practice medicine and you see a Parkinson patient by telemedicine over state lines, you can be charged with a crime. And insurance companies aren't going to pay for it.

That's expired now. We had warned that that could happen and that's exactly what happened. So, we took a huge leap forward in Parkinson's, and now we're backtracking and trying to get it back. But we've been advocating kind of upfront, proactively that we need to address telemedicine and address access for all people and in disparities. And then, of course, folks like me, we're scientists at heart. So, we have all sorts of things in my own laboratory. We're moving things in neurocircuitry, and in smarter neuromodulation technologies, and in other areas of Parkinson's disease. But there's lots of great researchers that are out there. Bastiaan Bloem is one of the world's best in gait and in walking. And, of course, Ray Dorsey, one of the best in thinking about the environment and prevention.

And so, I think each of the authors has really done a great service in inspiring people. But more than that, it's not about us. It's about the community. And so, trying to build this community to make a difference and think about what does it mean to end a disease, and what do we need to do to create a movement? And so, I think we've created advocacy, but we haven't created enough of a movement yet. And when we get to the movement level, we'll go from $200 million of funding, which is what we asked the White House and our red card campaign as part of this *Ending Parkinson's [Disease]* book. We asked the White House to go from $200 million of NIH funding or $250 million to $3 billion a year, which is what it took to move the needle for HIV.

So, we think we're going to need to increase by 10 or 15 times the spending. Increase that funnel so that we're bringing more therapies in. So, there's a lot to be done. I'm hopeful. I'm excited. I want to be proactive about it, but make no mistake, we have a lot to do if we're going to get there.

Marie: Well, Michael, I think you brought up some really excellent points in that response. And I know we've covered a lot of ground today. Is there anything else that you'd like to share with listeners as we wrap up our interview today?

Michael: Well, I would just say that for folks that have Parkinson's disease, one of the things that I always say is remember you should be hopeful, you should seek out some expertise, you should seek out the foundations, and with a good plan, you can have a great life. There's a path forward, and there's a plan for you.

And I'll end it by just saying I have a lot of folks that I've taken care of as a doctor for many years that feel like they have better lives after the diagnosis of Parkinson's than before.

Marie: Well, such an important message, Michael. We truly appreciate you joining us on the show today and sharing your expertise and insights.

Michael: It's my pleasure. Thank you for having me.

Marie: Oh, it's been so much fun to chat. And listeners. It's been great to have you here with us as well. If you want to know how The Michael J. Fox Foundation can help your research, please visit https://michaeljfox.org/researchresources. And you can find new episodes of this show each month on the MJFF website or on your favorite podcast platform. And when you have a moment, please subscribe to our show to make sure you don't miss out on the outstanding lineup of upcoming episodes. We look forward to connecting with you again in our next episode of *The Parkinson's Research Podcast*.