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 we share will advance your efforts and partnerships to improve brain health. We are welcoming guests with a range of experiences and viewpoints. The views expressed belong to the guests themselves.

Today we are excited to welcome our guest, Dr. Doris Wang. Listeners, Doris is a neurosurgeon and Associate Professor in the Department of Neurological Surgery at the University of California, San Francisco, or UCSF. Today we are excited to talk more about her work on neurosurgical interventions for Parkinson's disease and other movement disorders, which spans focused ultrasound, adaptive deep brain stimulation, and more. So, Doris, welcome to our show today. How are you?

Doris: I'm great. Thank you so much, Marie, for having me on the show.

Marie: Well we are excited to learn more about you and your work. And perhaps we can start with some background first. So, Doris, can you tell us a little bit more about your background and how you found your way to your current position there at UCSF?

Doris: Absolutely. So, since I was in high school I've been interested in the field of neurosurgery and neuroscience in general. I just remember taking an anatomy and physiology class in high school. Whereas we kind of have a basic understanding of how the other organ systems work, like the heart, the kidney, the lungs. There was just so little known about neuroscience and how the brain works and how it controls our emotions, our motor behaviors. And I just wanted to understand more about this enigmatic organ, which is so central to our being.

So, yeah, I just had the idea that I want to do neurosurgery because I thought I was pretty good with my hands and want to uncover the secrets of the human brain. So, I had this idea of going into college, and during my undergraduate years at Yale University, that's when I really got introduced to the field of neuroscience. Where I got to work in a neuroscience lab and got to record neurons firing. It was super exciting. And I also got to shadow neurosurgeons during my undergraduate years. And I just really enjoyed the OR environment and got a taste for what it's like. And I came to UCSF for my MD PhD degree. So, wanting to pursue and combine my interests in neuroscience and medicine. And

here I just have fantastic mentors along the way and never veered far from the school of becoming a neurosurgeon/neuroscientist. And you know, long story short, here I am, and I'm very fortunate to be doing what I'm doing.

Marie: Oh, that's wonderful. And I know, Doris, you're doing amazing work that I mentioned spans a couple of different areas or types of interventions for Parkinson's disease and movement disorders. So, perhaps we can start with focused ultrasound treatment first. I think this is a fascinating area. So, to get all of our listeners on the same page, Doris, can you first describe how focused ultrasound works and maybe the mechanisms that are involved?

Doris: So, focused ultrasound is a type of neuroablative surgery. So, what it does — it uses really high energy sound waves. So, these are more than just the sound waves that we can get an image of, you know, during the regular ultrasound. But what they do is we use really high energy, high intensity ultrasound. And just like a magnifying glass, you know, where they focus, we can increase enough energy to heat up tissue. So, that can be tissue throughout the body.

And back in 2016, this technology became available to treat brain disorders. So, basically patients, they're in this helmet shaped transducer that can produce up to one thousand twenty four ultrasound elements. And where the beams come together, we can accurately, very precisely heat up regions of the brain to the degree where we can create an irreversible lesion in the brain. So, it's called a thermal ablation. So, we use heat to oblate the brain tissue. So, in short, it burns a precisely placed hole in the middle of the brain. And as neurosurgeons, we place this lesion in areas of the brain that's involved with generation of tremors, for instance, or in the part of the brain that can help with some symptoms of Parkinson's disease.

Marie: Very interesting. And I think that was a great description. And can you touch on perhaps some of the advantages or maybe the limitations of focused ultrasound, compared to some of the other options that are available for patients?

Doris: Lesion-based therapy has been around long before deep brain stimulation, which is the other type of surgery I do as a neuromodulation technique. So, it has been around for a long time. But I think what's really unique about focused ultrasound is that it's very immediate. We don't need to drill any holes or make any incision in the patient. So, from the surgical perspective, it's not very invasive in that we're not cutting into the brain, cutting into tissue, or putting in any implants. But in terms of the brain, we are creating a permanent lesion in the brain. So, some advantages is that it's incisionless. So, for patients who have a lot of medical comorbidities that are not good surgical candidates, this is a great option for them.

Some of the downside — it is permanent, right? So, if we do cause adverse effects or have side effects, those could be permanent. Whereas DBS is adjustable. The other thing is if it loses efficacy, then it's hard to re-treat the same area. So, there's the lack of adjustability, whereas deep brain stimulation, neural modulation therapy has the advantage of.

Marie: That makes sense. And I understand there's a variety of different applications that are approved by the FDA- and also some non-FDA approved applications that this focused ultrasound treatment is starting to be used for. So, Doris, can you go into some detail on all of these different applications that you're seeing in the literature or in the clinic today?

Doris: So, starting with the FDA-approved applications, FDA has approved use of focused ultrasound thalamotomy to treat essential tremor and tremor-dominant Parkinson's disease. So, basically patients with action tremor (which is essential tremor usually), postural tremor, or Parkinson's tremor, who don't want to have DBS can undergo this treatment. And it's a common goal procedure. It usually takes a couple of hours, and patients go home, hopefully tremor-free. And also FDA has approved the use of a second side focused ultrasound thalamotomy to treat essential tremor. So, nine months after the first side, patients can come back in to get the other hand treated, which is really nice.

Besides focused ultrasound thalamotomy, FDA also approved the use of focused ultrasound pallidotomy. So, this is thermal lesion of the posterior segment of the globus pallidus interna to treat some of the motor symptoms of Parkinson's disease. So, that can include tremor, bradykinesia (which is slowness of movement), rigidity (which is stiffness), as well as dyskinesia. That's too much unwanted movement, which is a complication of taking dopamine medication. So, those are the FDA approved indications for focused ultrasound. And I think there are a lot of off-label uses. So, I know there's been studies using focused ultrasound to target the subthalamic nucleus, which is a common target we use for DBS to treat Parkinson's symptoms. And there are some other variations treating other areas of the thalamus to treat dystonia, tremor associated with other diseases like post-stroke tremor, multiple sclerosis type of tremor. I think those are under investigation, and the case reports are still pretty small, but they're showing promising results.

Marie: Phenomenal. Well, Doris, thank you for giving us some background for focused ultrasound. Can you tell us more about some of the work that you've been doing related to focused ultrasound?

Doris: Oh, absolutely. So, I think finding the sweet spot to lesion, that's a key, right? So, we want to target the best location that can treat an individual's symptoms without causing side effects. So, some of the techniques that we use at UCSF —

which is great because I partner this very closely with our neuroradiology colleagues — is we perform diffuser tensor imaging. So, using tractography to map out the white matter pathways, basically, which pathways we can lesion to safely improve symptoms without causing side effects. So, that's kind of from the clinical side. The other thing that's super exciting about focused ultrasound is, you know, So far I've been talking about using high frequency. So, again, this is high energy delivered aimed to lesion the brain.

There are also broad applications for low frequency focused ultrasound. So, this is less intensity. And what this does is it can do a lot of things. So, for instance, it can open blood-brain barrier. So, for brain cancer patients/oncology, one of the Holy Grails is trying to get the targeted drug to the right place without causing systemic side effects. So, there's a lot of clinical trials in this area in terms of using low frequency focused ultrasound to open up a blood brain barrier to enhance delivery of chemotherapeutic agents to the brain. Another consideration for the low frequency focused ultrasound is its potential to treat neuropsychiatric diseases, for instance, because low frequency can also perhaps modulate the neurons, causing a temporary lesion. And it's possible to even activate some areas. So, using it as kind of a probe to see which area to permanently lesion to improve things like depression, pain, addiction, for instance. So, I think there's a lot of exciting work in using this technology to probe how different brain circuits interact in causing disease states and how we can intervene to improve these symptoms.

Marie: Definitely. And I'm really glad, Doris, that you brought up this idea that it's all about location. I think finding that ideal location for applying this treatment is key, as you mentioned, but I think there's a lot of different dimensions to this. Really, it's not just sorting out the single XYZ coordinate point. It's also the size of the lesion, thinking about, like you said, the connectivity. How do you tease out this equation of what is going to be the best lesion size or shape that you're looking for for a particular patient?

Doris: So, it's very individualistic. Traditionally, we just kind of throw out a target that's tried and true and then test it around. Basically trying to see if I can reduce the patient's tremor, for instance, without causing slurred speech, or weakness, or sensory changes. But now I think with our targeted approach, mapping out individual pathways, we're able to arrive at that particular patient’s sweet spot a lot earlier. And I think this comes from a lot of research from multiple centers. I think by pooling this data across multiple institutions, across thousands of patients, then we can refine and define the best target for individual patients.

And perhaps we can even go into finer details, like finding what type of tremor, for instance. Do kinetic tremors respond better to lesions in a different area than postural tremors? So, there's a lot of granularity that we are just beginning to

explore. So, I think using a combination of advanced imaging techniques, tractography, and maybe even using connectivity, like functional connectivity, can really help us define and refine this technique for future patients.

Marie: And you mentioned earlier that the change in symptoms or the effects of this ultrasound are relatively immediate. So, Doris, can you talk about what you see in terms of the timeline of those symptoms? Do you see sort of 100% of a change right away? And then what are the data so far in terms of for how long these benefits or changes might be maintained?

Doris: So, the other advantage of focused ultrasound is at lower temperature. So, if we heat up the brain just a little bit, what it does is it creates a temporary lesion that lasts maybe a few minutes. So, we really take advantage of this system to kind of map out and test out what the best location is for a particular patient.

And when we apply this energy within a few, I would say about 10 seconds, or 11 seconds, then we should be able to see an effect if we reach about 50 degrees Celsius. So, the tremor reduction at that temperature should be immediate. And also the side effects should be pretty apparent. So, we use this low temperature test lesion to kind of map out where we want to be for permanent lesion. And then once we find a good location for a patient, then what happens is we increase the energy delivered to that spot to reach a higher temperature.

So, somewhere above 55 Celsius degrees. So, that would create a permanent lesion. And again, the effects are immediate. So, it's really exciting, actually. Somebody who's been trembling for decades. And then all of a sudden, after 10 to 20 seconds of treatment, their hands stop shaking, they're able to draw, write. That's really satisfying. I think out of all the neurosurgical procedures I perform, this is super exciting.

Marie: I think that's excellent. And do you have any data yet on the duration for the maintenance of these benefits after the ultrasound session?

Doris: I think the five year results have been published. So, we typically quote patients about 80 to 90% immediate tremor improvement. And some tremor may return within the first year, usually, and drop off slightly after that. And the most recent evidence I've seen is about, on average, 70% tremor improvement in five years. So, the effect may last a lot longer than that. And of course, this is dependent on the size of the lesion. So, the larger the lesion, the better, I guess, or more durable the effect.

But then we kind of had to balance that with the side effects. So, a larger lesion means that we may be encroaching on areas that affect a patient's balance, a patient's sensation, or even their strength. So, it's always a fine line between

applying enough energy, create a large enough lesion. We aim to create about like a five millimeter by seven millimeter of lesion here. So, yeah, that's kind of the ballpark we're aiming for. But yeah, it's always depending on the patient's anatomy and their symptoms.

Marie: And I believe you mentioned also that once a patient is treated with this approach, it's difficult to kind of go back in, whether it's re-lesion or change the lesion to adjust it afterwards. So, what are some of the reasons why it's maybe not recommended to do this? Or it can introduce some challenges.

Doris: I think you have to kind of see why somebody's tremor returns after, I would say, failed focused ultrasound. So, if you image them and it looks like the initial lesion, it's not as large as you want it to be, then I think that's a great candidate to get re-treatment. And in that case, yeah, you can just apply more energy, and you hope we can expand that lesion that initially had worked, but failed later. But I think some of the challenges could be scarring, also known as gliosis around the original lesion. So, the thermal heating of a previously treated lesion may be more variable, unless predictable. So, you have to really be careful of side effects.

And then the other thing is what I found in our experience after treating one side, So, when we're treating the second side for patients, for some reason, their heating is less predictable and a lot of this has to do with their skull density ratio, So, SDR. So, to qualify for focused ultrasound, we do a CT scan for patients and their skull density has to be above 0.4.

And this is just a prediction. Basically, we don't want their skull to absorb all the energy we're applying so that their brain cannot heat up to the temperature that would result in a permanent lesion. And there are some thoughts that after even first side treatment, that the skull behaves in a different way. That makes heating of the second side a little less efficient. So, I think that could be another potential challenge to retreating somebody, especially somebody with a low SDR, who's borderline in the first place. So, it just may be more technically more challenging and more painful or uncomfortable for patients to re-treat the same side.

Marie: Well, thank you so much for diving into some of the details of the amazing work that you're doing in focused ultrasound. I'd like to change gears next, and we can talk about deep brain stimulation. So, I know Doris, you are doing wonderful work in this area as well.

And we'll start by acknowledging, perhaps, that in what we call “traditional” deep brain stimulation surgery, the patient is awake and responding as needed to really help ensure the optimal lead placement without impacting things like language, et cetera. But that isn't the only available approach. So, you actually

have experience doing this procedure called “sleep interventional MRI-guided deep brain stimulation”. Can you first explain this procedure and how it differs from the traditional awake, alert DBS surgery?

Doris: Absolutely. I was fortunate enough to train at UCSF where this technique, the interventional MR-guided deep brain stimulation was born, actually. It was developed by my mentors, Philip Starr, Paul Larson, Alastair Martin. So, unlike traditional awake DBS in which we kind of have to have patients be awake for the testing part to make sure we're in a good location. Since again, DBS is based on drilling a small hole, implanting a lead. So, during this whole process, we can not exactly see, you know, through a patient's brain to see where the lead is landing, relative to their brain structure. So, that's why we need patients to be awake. Just an additional way of confirming we're in the right place.

We can now take this whole surgery and perform it in a kind of conventional MRI magnet. So a patient can be completely asleep under general anesthesia. And what we're doing is using image guidance to place a lead. So, this takes advantage of an advanced imaging technique that has been developed. So, now we have image sequences that can really delineate clearly what the deep brain targets that we typically implant for surgery. So, these include the globus pallidus interna (the GPI) or the subthalamic nucleus (the STN), and using these sequences, we can visualize them clearly. And we can take images in real time as the leads are going into the brain.

So, now we know exactly where the leads are ending up, just based on the imaging. So, therefore patients don't need to be awake for the procedure. This has several advantages for patients who can't tolerate being awake for whatever reason, for anxiety, for language barriers. This really widens the access to DBS surgery. And then the other thing is with awake surgery, we typically have patients come off of their Parkinson's medication because we want to see the efficacy of DBS in treating some of their motor symptoms immediately in the OR. With this technique, because we can get the lead usually within half a millimeter of our intended target, patients don't need to even come off their medication. So, overall, I would say patient comfort is a lot better with this interventional MRI-guided technique, rather than the awake technique.

Marie: Certainly. And I know you relatively recently published some data on the outcomes, basically comparing the outcomes of this newer procedure, this interventional DBS approach to the traditional awake DBS surgery. So, Doris, can you talk about what you've seen in terms of any differences in outcomes?

Doris: So, we did a retrospective review of all the surgeries done at UCSF with the asleep technique versus the awake technique. And this is multiple surgeries done by Dr. Paul Larson and Phil Starr. And we basically saw no difference in terms of

clinical outcome, in terms of improvements with the motor rating scales after surgery, or in terms of medication reduction. Basically, patients did equally well. And there's no changes in even adverse effects like infection, bleeding. So, this retrospective study highlights the fact that interventional MRI guided DBS is equally good as the traditional technique.

Marie: Absolutely. And I think those are phenomenal findings because it gives a neurosurgeon a little bit more flexibility in terms of determining what may work best for an individual patient or for centers to know that what they're doing is perhaps still a reasonable approach. But let's talk about, as a neurosurgeon Doris, you make some of these key decisions when you're working with a particular patient and their family. So, what are some of the key considerations that you're weighing in your mind when you are recommending a particular neurosurgical intervention in terms of thinking about, whether it's focused ultrasound, or whether DBS is the answer, or maybe something else entirely?

Doris: I think it has to do with what is a patient's most bothersome symptom. So, for essential tremor, DBS and focused ultrasound can equally be good in terms of suppressing tremor and limiting side effects.

So, then I kind of look into the patient's medical history. If it's somebody who's elderly, who for instance has a lot of medical comorbidities, which make implant surgery or surgery with incision and general anesthesia high risk, then I probably would lean towards focused ultrasound. But if it's a young patient with super severe tremors with tremor that may progress or tremor that's slightly atypical or involving head, neck, or voice, then perhaps DBS has better efficacy or longevity than focused ultrasound. So, it's always a discussion with a patient. For patients with essential tremor, whether to go for a neuroablative therapy or a neuromodulation therapy like DBS.

And then the other thing is, you know, considering patients' lifestyle. So, if it's somebody who's really active who doesn't want to seem like they have surgery or who doesn't want to maintain a device. And maintaining a device means either recharging it or going to a neurologist for fine tuning their device. Then the focused ultrasound is a great treatment option for them. So, all these factors come into play when deciding which one to recommend. And I think patient preference goes a long way in deciding focused ultrasound versus DBS for essential tremor.

Now for Parkinson's disease, I still think for most patients with Parkinson's disease, if medication is no longer working that well, and they start developing motor fluctuations. So, that's when after they take their Parkinson's meds, they can move freely, do pretty well. But sometimes they may have dyskinesia, So, a side effect of medication. And then the medication just stops working. They have

to take 10 doses of medications throughout the day. DBS is a wonderful therapy. And I still think that's kind of the gold standard because DBS can treat both sides of the brain. We can treat a lot of these symptoms like slowness, rigidity, any symptom that's improved with medication, DBS can essentially help.

So, for those patients, DBS is a great treatment for Parkinson's patients. And I think the granularity goes into, for instance, if a patient is not a candidate for DBS surgery, and then what are their main symptoms? So, if, for instance, you have a Parkinson's patient who's elderly, like say, 80s or in their 90s who don't have great health, and their main symptom is really tremor, whereas the other symptoms like slowness, stiffness is relatively well-controlled with medication, then I think focused ultrasound thalamotomy is a great option to treat tremor in one of their hands.

And if you have a patient with Parkinson's disease, who is not a good surgical candidate, but their symptoms are fairly asymmetric, then focused ultrasound pallidotomy may be a good option for them. Again, it's a constant conversation and discussion with a patient, their preference, their neurologists, and their family members to kind of weigh the benefits, alternatives, and risks of each procedure.

Marie: Definitely. And then in talking about DBS, maybe Doris, once you make that decision that deep brain stimulation is the direction you're going to go with a particular patient, how do you then make the decision of awake versus asleep DBS surgery?

Doris: For essential tremor, I'm still doing all of them awake just because I need that testing. Even though now we have a lot of really advanced and great imaging techniques. So, some of my colleagues are starting to do essential tremor, target the VIM areas of the thalamus asleep using IMRI, but I still do mine awake. And now for Parkinson's patients, then the question is awake versus asleep.

So, I kind of usually get a sense from talking to the patients, their preference, their anxiety level about surgery. So, for somebody who's kind of risk aversive, who doesn’t like the idea of being awake, or who has a lot of symptoms for which being off medication would make them extremely uncomfortable, like when patients have dystonia. So, that's like where their muscles get really tight, crampy, can be really painful. Then awake DBS is not a great option, because they're in pain, they're uncomfortable, and surgery is not meant to be torture.

Marie: Right.

Doris: We want surgery to help patients while they're comfortable. And that would give us actually the best testing results as well. So, for those patients, I would definitely recommend getting asleep DBS. So, some of the things we do at our

center that may bias the decision for a patient is that for awake DBS, since we do these procedures in the operating room, I can then implant not only the electrodes that go into the patient's brain, but also the connection wire. So, that's a lead extender, and the pulse generator in the chest, in one day. So, basically in one surgery, they're getting two for the price of one. They can get all their hardware implanted if they go the awake route. For asleep, we do stage them just because the second stage surgery involves equipment that's not compatible in the MRI. So, that may change a patient's decision based on purely logistics.

Marie: Oh, that makes sense. And thank you for walking us through it all. And I know we've talked about DBS as just sort of one category that a patient may choose for treatment, but there are actually a lot of different ways that DBS can be delivered. And I'd love to spend some time talking about adaptive deep brain stimulation. I think this is a device that's using a sort of self-tuning mechanism to try to provide more flexible or maybe more personalized treatment. So, can you go into some detail, Doris, about how this adaptive DBS works and perhaps what parameters you can leverage or use in the self tuning process?

Doris: So, this is a super exciting area and advancement, I think, in neuromodulation therapy. So, current DBS, as you mentioned, just works by using continuous high frequency stimulation that's set by the neurologist. So, we can set basically three or four parameters, which is the amplitude we're delivering electricity through, which contact on the electrode we're delivering through, the pulse width, and then also the frequency. So, there are so many parameters that we can explore.

And everything is kind of based on trial and error. Finding the optimal setting for the patient. So, the adaptive DBS, the idea is that we can now use patients' brain signals to fine-tune DBS. So, while DBS works great in reducing, as I mentioned, these motor fluctuations, so the ups and downs of Parkinson's disease. One thing we have to keep in mind is that the up and down is a lot of times determined by what the patient is doing, what they're eating, how long since they took their last dose of medication. So, for instance, the patients who just took their medication probably don't need quite as much stimulation to see benefit. And in fact, if they have stimulation plus a regular dose of medication, that again can drive some of the side effects like dyskinesia. So, the whole idea of adaptive DBS is — use patients' own brain state to control stimulation.

Usually it's in the realm of amplitude. And that's a space that's being explored right now. But we can easily change the frequency of stimulation, pulse width, or change a lot of other different parameters. So, right now, there's been a few different clinical trials in exploring the use of a biomarker for slowness and rigidity in the beta frequency band. So, that's about a 13 to 30 Hertz brainwave that's found in the basal ganglia in the STN and GPI of patients with Parkinson's disease. And there's been a lot of study based on work from our center and

others that suppressing beta oscillation in the STN or GPI is associated with improvement of motor symptoms in Parkinson's disease.

So, there's a lot of work on using the amplitude of this 13 to 30 Hertz frequency wave in the brain to control the amount of amplitude or amount of stimulation that's going to that patient. On the other hand, there's a lot of work done by my colleague Phil Starr, who's a real pioneer in the area of adaptive DBS, to find a marker for an abnormal state. So, a complication of DBS — dyskinesia. So, he found that this biomarker in the gamma band, So, 60 to 80 Hertz range, is associated with too much unwanted movement. So, then we can use that biomarker to control DBS by lowering the amount of electricity that's going to a patient. So, we can use both positive symptoms of DBS and negative symptoms to kind of control the amount of stimulation. So, that's one area of adaptive DBS that's probably getting pretty close to being available for patients.

Marie: Oh, that's really exciting. And I know you've been working to identify some gait-related biomarkers as well that could potentially be used to drive adaptive DBS. So, Doris, can you tell us more about your work in this area?

Doris: Yes. So, this is my own research on gait-related biomarkers in the realm of adaptive DBS. So, while DBS is really great at improving tremor, rigidity, bradykinesia, it's not so good at treating gait disorders, especially advanced gait disorders like freezing of gait. And I think this has been a large source of frustration for patients as well as for providers.

How can we take advantage of advanced neuromodulation to treat gait disorders? Some of my own research is trying to use brain biomarkers of gait. So, when a patient is about to swing their left versus right leg to control level stimulation independently. So, we can, for instance, stimulate the left brain a little bit higher while they're taking a swing with their right leg and vice versa. And through this paradigm, what we're hoping to achieve is to restore some of the natural phenomenon that happens while somebody's walking.

So, what we found is that when somebody walks, and of course, this research is done in patients with Parkinson's disease, that some of these frequency bands in the brain actually oscillate in accordance with the gait cycle. So, this is probably what's considered a more normal pattern of brain fluctuations that occur with gait. So, what I'm trying to do with adaptive DBS is to basically recapitulate, kind of, these more normal gate patterns that occur in the brain and try to see if we can use that to improve gait and also maybe prevent freezing of gait.

Marie: I think this is tremendously exciting. And I know, Doris, that it's still quite early in the research in terms of the timeline in this specific area. But have you seen data so far — or maybe have you run into the problem yet — where the signals you

might be getting from different biomarkers are kind of competing, right? Where one thing says, okay, well, to improve gait, maybe you need to turn up the amplitude but the other biomarkers are saying, to fix the problem maybe in tremor, you have to turn the amplitude down. So, you have to make this decision or prioritize one over the other.

Doris: Yeah, absolutely. So, that's one of the things we're testing to see if we implement this kind of what we call fast ADBS. So, basically, they're changing states constantly within milliseconds, whether we worsen some of the symptoms of their Parkinson's disease. So far in our preliminary testing, and this is hours of testing a few patients, they haven't actually noticed too much changes in their other Parkinson's symptoms while we're implementing this adaptive DBS. And then one of the other adaptive DBS strategies that we're employing is find a parameter that's optimized for walking. So, then we can switch between the parameters that's optimized for tremor, for instance, while they're sitting around eating.

And then when they get up to walk, switch it to a different set of settings. So, there are multiple strategies we can employ with adaptive DBS. And I think that's what makes this work really exciting. And also there's so many things we can explore. So, I'm very excited about the potential of this therapy and improving some of these harder to treat Parkinson's symptoms.

Marie: Absolutely. I think the research in this area is tremendously promising. And I'm curious, what have been some of the biggest surprises or maybe the unexpected outcomes that you've encountered so far in your research?

Doris: So, as I mentioned, we're changing stimulation amplitude, right, pretty rapidly from the left and the right brain. One thing that's a little surprising is that patients can't feel it, they can't tell. I would sometimes expect, you know, a patient can feel and can tell whether they're in the adaptive setting or continuous stimulation. But surprisingly, patients haven't been able to tell that, which is great. That means this doesn't affect them or doesn't distract them.

And then the other thing is, in our very short clinical testing, in our very preliminary data, we see that this kind of adapted DBS, we don't have to capture every single step. So, even if we're changing stimulation in three quarters of a step, we can improve some of the things like step length symmetry between the left and right leg compared to their clinical DBS, which is really interesting. So, that suggests that perhaps continuous DBS actually limits the brain's ability to reflexively change in response to, for instance, the environment. And that we kind of need to give the brain a break, so to speak, while a patient is walking and while they're trying to engage in adaptive behavior.

Marie: Very interesting. And is there anything else, Doris, that you would like to cover in terms of research that we haven't touched on yet before I switch gears once again?

Doris: Some of the other things that's being explored with adaptive DBS is to treat non-motor symptoms of Parkinson's disease. So, so far, we've all focused on motor symptoms. And we tell patients, right, if you have depression, anxiety, that's part of the Parkinson's disease. DBS may or may not help it. Usually it doesn't help. And there's some evidence that perhaps stimulation of certain areas can exacerbate mood symptoms.

So, I think there's a lot of exciting things about using adaptive DBS. So, it's the first time we can actually sample chronically from a patient's brain, the brain waves associated with different motor behaviors and also different moods, cognition. So, I think with this exciting technology, we can actually use that to understand a lot more about the human brain. So, the emotional control circuits, the cognitive circuits, the limbic circuits, I think that's also really promising.

Marie: Certainly. And I'd love to talk about tools, and resources, and collaborations as well. I think in order to do this exciting groundbreaking research, you need to have the right tools and resources available. So, Doris, can you talk about the things you're seeing that are really advancing or accelerating the field and helping move your research forward?

Doris: So, none of this work is possible by oneself. So, it's team science at its finest. For instance, in my own group, my lab is comprised of biomedical engineers, I have programmers, I have physical therapists, I have neurologists all working together in terms of carrying out this research. And some of the really exciting collaborations we form through the research is partnering up with device companies that make external devices that can track motion.

So, as you are aware, you know, Apple Watch, iPhones, and also sensors, can really capture gait kinematics, what people are doing at their home environment. And this is a really powerful tool when we couple that with the ability to record brain activity long-term using these devices to really decipher what the brain is doing. So, I think that's an important key element in moving the field forward.

And also, I think there's a lot of unknowns in terms of using these novel devices. So, I'm part of, for instance, Open Mind Consortium, which is a group of investigators who are all using these bi-directional neural devices to study various diseases, disorders, and so we can give each other tips about technical challenges, codes, and programs that somebody has written to help advance the research or help with the data collection. So, it's been really fun to be able to work with people across all these disciplines towards a common goal.

Marie: Oh, I think that's amazing. And I think you're absolutely right that these collaborations are key to moving the field forward. So, Doris, are there any specific tools, or resources, or collaborations, or even previous research funded by The Michael J. Fox Foundation that have been particularly helpful in the work that you do?

Doris: Oh, yes. So, my main project of investigating gait-related biomarkers that can drive adaptive DBS for gait is fully funded by The Michael J. Fox Foundation through their Therapeutic Pipeline Program. They provided a lot of resources for me to carry out this research. And they also provided a lot of tools in terms of posting these trials online for patient recruitment that was really invaluable. And finally, I think the Advisory Committee during our checkup meetings will give me really great ideas and avenues to explore in my own research. So, it's really valuable to have this funding and the support from The Michael J. Fox Foundation.

Marie: Definitely. I appreciate you sharing that. And I think that's something where people don't necessarily realize that The Michael J. Fox Foundation, their support goes beyond just research funding. There are all of these other ways that you can interact and benefit from interacting with the organization.

Doris: Oh, Absolutely.

Marie: And I know we've touched on some exciting new directions and discoveries a few times throughout our conversation. But Doris, what do you see right now as the most promising future directions or maybe the biggest areas of opportunity in Parkinson's disease research?

Doris: Well, that's a great question. So, there's so many directions. I can't speak too much about the biomarker or the genetics, but I think from the field of neuroscience and neuromodulation, just being able to sample and study the whole brain circuit in the real life environment, I think that's a really exciting opportunity. Before we're restricted to studying diseases in a clinic, in the laboratory, and the ability to kind of carry out what's happening out in the real world when a patient is encountering problems or something's going particularly well. Being able to study whole brain circuit networks that control, again, these naturalistic behaviors, I think is really exciting.

Marie: Definitely. And I'm looking forward to seeing future developments in this area, both from your group as well as others around the world. And I'd love to conclude, Doris, if we can by talking about how your work is bringing us closer to finding a cure for Parkinson's or contributing to improved therapies for people who have Parkinson's today.

Doris: Yeah, some of the things we're getting closer to is finding both naturalistic biomarkers of good gait and then also pathological biomarkers of gait, like freezing. So, again, once we identify those signals that are working well when a patient's walking in Parkinson's and also when they're not walking well, then we can use DBS to enhance those good signals and then also disrupt those bad signals. So, I think we're a lot closer in finding potential solutions to this really complex problem. And I think that's really exciting for not only myself, but also maybe for the future of Parkinson's research.

Marie: Well, thank you for giving us insight into all of the outstanding work that you are doing in this area. And Doris, we appreciate you joining us on the show. So, thank you so much for your time today.

Doris: Thank you so much, Marie, for having me.

Marie: It's been a pleasure to chat with you, 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 michaeljfox.org/researchresources. And you can find new episodes of this show each month on the MJFF website or on your favorite podcast platform. When you have a moment, please subscribe to our show to make sure you don't miss our outstanding lineup of upcoming episodes. We look forward to connecting with you again in our next episode of *The Parkinson's Research Podcast.*