BroadcastMed | Deep Brain Stimulation for Movement Disorders: Clinical Treatment and Current Research

DR. ROBERT IZOR: you all for attending. I'm Dr. Izor. I wanted to just take a minute to thank Dr. Whitmer for actually helping to start this research effort. I also thank the NeuroTexas Institute and St. David's. We often get bogged down with clinical work. And it's sometimes difficult to spend time especially doing basic science research. And this is a nice opportunity to look at some of controversial issues that have arisen in recent years with regard to cognitive dysfunction, specifically related to deep brain stimulation and Parkinson's disease, but also other cognitive behavioral aspects that may be related to deep brain stimulation. So today, we're going to split this talk up into three sections. It may move a little rapidly. I want Dr. Whitmer to have enough time to approach her research interests. So I'm going to get started now with the surgical management of moving disorders. So we mainly focus on three major conditions-- Parkinson's disease, essential tremor, and dystonia, when we're talking about neuromodulation and deep brain stimulation. There are other interests that are currently being looked at including psychiatric conditions from depression to obsessive compulsive disorder. But we're going to focus mainly on these conditions as they are the largest percentage of patients in my practice. Parkinson's disease-- I'm not going to go into too much detail as to what that is. Hopefully most of you know this. It's a progressive neurodegenerative disorder. It's characterized by four major criteria, which is resting tremor, rigidity, slowness of movement, and postural instability. And there's a wide variety of how patients present with Parkinson's disease. Some present mainly with tremor for many, many years and have very little cognitive or behavioral issues. Whereas, another large percentage of patients have a lot of non-motor issues including depression, apathy, psychiatric disturbances, hallucinations. And so it's just important to recognize we're dealing with a wide spectrum of disease. This is a slide showing the pathology we normally see in Parkinson's disease, the Lewy body, which lives inside the neurons. There are other neurodegenerative disorders that involve Lewy bodies, such as multiple system atrophy, and that primarily affects glial cells. It turns out deep brain simulation doesn't usually help other disorders like multiple system atrophy nearly as well as Parkinson's disease unless we're looking for specific features such as tremor control. So essential tremor and other dystonic action tremors are another large percentage of patients we consider for DBS. There aren't really pathological correlates very well described with essential tremor. They've done a lot of brain cutting studies on essential tremor patients and have never really found consistent findings that demonstrate pathology. There are some articles that suggest that a certain layer in the cerebellum may be affected. Some of these older patients, sometimes they'll find Lewy bodies in certain parts of the brain, but nothing consistent. But tremor, not necessarily from Parkinson's, but tremor in general is probably the largest movement disorder we see, affecting about 7% of the population. Most patients with either action tremor or resting tremor is not necessarily that disabling. So we end up offering DBS more frequently to patients with Parkinson's disease than patients with essential tremor. Unfortunately the title to the slide fell down to the middle, but these are pictures of patients with dystonia. This is even less well understood than essential tremor. Dystonia can be a primary consequence from genetic or hereditary influences. In deep brain stimulation, DBS is the treatment of choice for primary generalized dystonia or DYT1. It also seems to have good effect in some pediatric cases of cerebral palsy and perhaps other genetic dystonias. There are secondary dystonias that occur from things like head trauma, stroke, multiple sclerosis. Those conditions are usually less predictable as to outcome. About half the time, we don't necessarily see benefit with DBS with secondary causes. And even with primary causes, the benefit from DBS is not as profound as what we see with essential tremor or with Parkinson's disease in most cases. So what is neuromodulation? This defines a new modality that has been around for, I would say, about 15 to 20 years-- more mainstream in the last 10 years. I think a lot of this was developed through following stroke research when patients would have a stroke, they'd say they have Parkinson's disease and develop a stroke in the STN, or the subthalamic nucleus, and then all of a sudden, their tremor, and rigidity, and slowing would improve dramatically on the contralateral side of the body. So I believe was in France, they decided to start doing these surgeries where they would burn holes in these targets on purpose to try to relieve symptoms. And while they were doing that, they realized that the electrical field that they generate to burn the hole would actually control the symptoms before they actually burned a permanent hole. And that led to the idea, well, why don't we just leave a wire there that can generate a lower power electrical signal and alter the data that's coming out from that part of the brain, thus controlling symptoms? So that defines what pallidotomy, thalomotomy. Pallidotomy is what Michael J. Fox had to control his Parkinson's initially. And DBS, depending on where you burn the hole, you might ruin an opportunity to use DBS at another target because quite often the output from a nucleus, in this case, the STN, the output to that nucleus is the globus pallidus. So we'll talk about targeting in a minute. Stem cell transplantation, there's been some research done where they're actually placing stem cells in the striatum, and in animal models, where they're placing it actually in the nigra. And we're seeing variable responses there. Some of the more impressive results seem to wane after a few years. And then there's a question, well, do you have to reimplant stem cells every few years to maintain any kind of benefit? And then there have been some attempts that resulted in violent dyskinesias. So we're not convinced that stem cells are going to lead us to an answer, at least at this point. Growth factor infusions, also involve stereotactic surgery, placing catheters into the brain. There was a trial performed in England where it appeared to provide quite a lot of benefit to these patients. But it just wasn't practical. We're not quite sure why that trial was ended. But it's not readily available, at least at this time. There's a new company, I think, that has the patent for glial-derived, neurotrophic growth factor that's looking at bringing it back. Also at the last neurology conference, I know they were talking about creating cell lines that will produce growth factors, protect those cell lines so that you can implant them into the abdomen so that they release, for example, brain neurotrophic growth factor, which can pass through the blood into the brain. So those are interesting areas for future development. So what makes us decide what target to use? In Parkinson's disease, the circuits are still not completely understood. The motor cortex, the pre-motor area, and the sensory areas all pass data through the basal ganglia, through the caudate putamin. And these circuits, the deep gray matter structures, are involved in helping to modulate the muscle tone at rest, the involuntary positional sense and muscular tone of the body that helps hold your posture and help to modulate smoothness of movement when you voluntarily try to do things. And so this figure just shows what some of the interplay is. All of these structure seem to interact with each other. The main targets that we use for Parkinson's, the subthalamic nucleus, right here, it seems to control both tremor, rigidity, and slowness of movement, and even postural stability, at least in those patients to respond well to medication. The outputs of the subthalamic nucleus is the globus pallidus. This is another target that's often used in Parkinson's disease, more so in the last couple of years, because of concerns that the subthalamic nucleus target might contribute to some cognitive deterioration in a small percentage of the patients. The globus pallidus has not been studied quite as well. And I've seen studies that show that some of the patients who undergo globus pallidus surgery also have cognitive decline. So it's not certain that this target is necessarily safer from a cognitive point of view. But in those patients who have notable cognitive decline, but they're not candidates for other therapies, and their symptoms are severe, there are some centers that are targeting the globus pallidus in preference over the subthalamic nucleus. Now the thalamus is a nearby structure. This doesn't say VIM, but it's very close. It's actually right above the subthalamic nucleus. And the thalamic target for tremor, the VIM, does not seem to control tremor-- I'm sorry, I take that back. It doesn't seem to control rigidity, or slowness of movement, or postural control, but it does control tremor very well. And initially, when Parkinson's patients had severe tremor, that was the target of choice until it was found that the STN actually did a very good job of controlling tremor and the other features of Parkinson's disease. So there are other targets that are being considered for other disorders, but I'm not going to go into to that today. So this is what a pallidotomy looks like. And it's basically just burning holes, causing a stroke. It's destructive. It's irreversible. It's fixed. You can't adjust it. And if you're off a little bit-- obviously you're near important structures, pyramidal tracks-- you can have permanent complications. So we're getting away from that. Deep brain stimulation, it does create some trauma as the lead goes to the target. And there are interests in finding a modulators, drugs that might minimize some of that trauma. But it's not a lot of trauma. And the fewer passes that we make doing this procedure, I think, makes a difference. Some centers do multiple passes, trying to map the target to see if they can find all of the clues necessary to hit the sweet spot, if you will. But they're creating a lot of passes through the thalamus and important brain structures. And our center, we don't feel that's necessary. We found a very good routine that seems to provide a very good results while minimizing passes. This is what the electrode looks like. There's two different kinds. The contacts are a little closer together. These are about a half a millimeter apart. These are one and a half millimeters apart. Contacts in both of these leads are about one half millimeters in width. And the lead itself is about one millimeter wide. So this is the main lead that gets left at the end of the surgery. We use a thinner wire that's just a monopolar wire

that we use to actually listen to the brain as we're approaching the target. And we also use the same wire to stimulate to test the site before we commit to placing the largest lead. We think that minimizes invasiveness and allows us to get better results. Once we pass these larger leads into the brain, it's harder to fine tune. If you have to move it, you've created a bit of a chasm-- or not a chasm-- a thin avenue where if you make another pass, you might fall into the same trajectory. So DBS, the data is pretty compelling. Now, in the right candidates-- patient selection is very important-- you can significantly impact their quality of life, improving motor function and non-motor features. Significant-- at least STN DBS-- significantly reduces the need for medications. It decreases and often eliminates dyskinesias, which are motor complications from drug therapy, provides very good tremor control. In fact, some essential tremor patients, a small percentage of them, become resistant to thalamic stimulation. And we may even consider the STN target as a secondary target. We've had some patients that get better control of tremor with the STN simulation in that area than they do from the VIM. In Parkinson's, it increases on time, at least by six hours. Most of our patients, with well-place leads, they don't really notice off states hardly at all. On much lower medication, they're pretty much the same all day. And they have better on state motor control than they ever did before DBS on their best medication therapy. Now that's not to say that DBS is perfect for everyone. In some Parkinson's patients, you give them medication and you don't really see adequate benefit. They're not really responding, usually with regard to gait function. And in some of those patients, if you performed DBS, they will get worse no matter what you do. We have seen some patients, though, that have gait freezing, that didn't respond that well to medication, where we performed the surgery and they did very well. So it just adds a certain element of uncertainty comparing who is the best candidate for surgery to another patient who may be not quite as good of a candidate. And so we try to lay out those risks to the patients and families. So it improves quality of life of both patients and caregivers. Greater than 60% improvement at two years. There are several cases of essential tremor. Patients with essential tremor are at higher risk for developing Parkinson's disease. It's not quite sure what the percentage risk is, but we do see it more frequently. And in those patients who have both an action and postural tremor, sometimes for decades before developing Parkinson's disease, that it also controls their action and postural tremor. The psychiatric phenomena that we see we often see in Parkinson's patients that is aggravated by their medications, because we are able to dramatically reduce their medication requirements, a lot of those problems go away. So there are differences between STN DBS and globus pallidus and VIM. But I want to show you some videos of a couple of Parkinson's patients just to illustrate the power of the therapy. Can someone start the video for me? So this is one of my early patients from about 2005. He is currently off of medication. And you can see that in his left arm he's a little slower than he is on the right. And he's more stoic, masked facies. And most importantly, off of medication, he cannot walk. He can't stand up or maintain his posture reflex at all. Many years ago, we would have been very reluctant to consider him for surgery, except that in the on state, on medication, he recovers this function. DOCTOR IN VIDEO: Can you hold yourself in place? Not at all? So you will fall if I don't hold you, right? DR. ROBERT IZOR: So this is the same patient on medication before DBS surgery. You can see some of the motor complications. It's mild this day. He has dyskenisia in his head and neck. But you can see that his motor function has improved dramatically on his left side. So he is responsive to medication. His main problem is that the dyskenisias are quite bothersome to him. And he also has significant off cycling multiple times during the day, where he's not able to walk. He's a fall risk. And the medication just isn't enough to keep him going. So this is still him on medication. You can see that he can walk. He has dyskenisias in his head. Now this is after surgery on no medication. This is probably about a month or two after surgery. And you can see that he's standing, good postural reflex, good fine motor control on the left side. And his gait and balance are quite good. So this is a case of a patient who actually did better, in terms of overall motor function, overall cognitive behavioral performance, after DBS surgery than his best medications could provide. And he does not have any tremor. All right. So DBS for Parkinson's patients without tremor is a realistic treatment option. So let's look at the next video. This is a tremor dominant patient. And unfortunately, he couldn't tolerate any of the oral medications. All of the Levodopa preparations caused headaches or behavioral disturbances. So he's already had the surgery. And I'm simply turning it off so that his tremor comes out so we can see it. And as with many tremor dominant patients, he doesn't really have significant gait involvement, at least not yet. DOCTOR IN VIDEO: Now can you try to tap your right finger? DR. ROBERT IZOR: So with DBS off, you can see that he's become more rigid in his facial expression. DOCTOR IN VIDEO: And his neck is more rigid. PATIENT IN VIDEO: [INAUDIBLE]. DOCTOR IN VIDEO: Can you turn your head? It's slower. And then try to walk over there and back. The effect of stimulation lasts a period of time. DR. ROBERT IZOR: And sometimes the stimulation effects can last hours. So patients with rigidity, postural instability, gait problems that are treated with DBS, sometimes it can take a day or more before they really turn off. So we're just going to turn the DBS back on. And it's instant relief. All right. So there's a case to be made for considering GPI as an alternative to STN. We don't currently perform very many GPI cases with our team. We've done about four GPI cases, all for dystonia. We haven't had any GPI cases, yet, for Parkinson's disease. It just hadn't been much of an academic interest for us because with well placed STN leads, we weren't really seeing any cognitive or behavioral issues except in a small percentage of patients, usually patients who had issues going into the surgery. But there is renewed interest, now, since some centers have demonstrated that there are some problems with verbal fluency with STN DBS. So I already explained about dystonia and GPI and the benefits with dystonia aren't as predictable. So one of the most important take home points of GPI surgery for Parkinson's disease is that it doesn't allow for reduction of Parkinson's medications in most instances. So those patients who have cognitive or behavioral issues related to their medication or a lot of motor fluctuations-- it does help motor fluctuations and dyskenisias to some extent, but it doesn't allow for reduction in medication. Now there's a lot of controversy as to, well, why is it that STN causes cognitive issues, particularly verbal fluency, and GPI does not? There was an article, recently published out of Spain, that suggests that it may be because we are reducing their medications. In that study, they demonstrated that if you reduce medications in Parkinson's patients, that diminishes verbal fluency. Not only are you slow in your movement, you're slow in your thinking and your processing in many different cognitive and behavioral areas. So as far as DBS for tremor, this has been studied for many years. This data is from several years ago. In our experience, patients who have DBS for essential tremor have continued benefit for many, many years. Out 10, 12 years now, where these patients continue to have significant benefit from DBS that's independent of medication. And quite often, patients can stop their medications that they use for the control of action and postural tremor. Now there has been a study that seems to show that they don't notice a lot of progression in essential tremor over time in those patients who have DBS. But in our experience, in my practice, I have seen evidence that the tremor does get worse over time. And you have to modulate stimulation to control that tremor, sometimes increasing the energy level or adding additional contacts. So problems with VIM DBS, placement of the lead, again, is crucial. The nucleus itself is actually fairly large. Maybe, in terms of DBS sizes, five, six millimeters wide, three or four millimeters across. And the lead going through the target-- you're basically putting a one and half millimeter trajectory path through the target. Well, the structures that live in that target include the tongue, so if you're not carefully testing the patient with stimulation during the surgery looking for side effects, these are things you may not pick up until they're in the office. And then it becomes a struggle trying to find stimulation parameters that control the tremor without affecting speech or causing pyramidal signs, pulling on one side of the body or the face. So essential tremor sometimes presents-- we don't call it essential tremor. We'll call dystonic tremor. But they're probably variants of the same condition where patients will present with primarily head and neck tremor. And I remember earlier in my training, we weren't so sure that it would be helpful for that. But since then, it's become pretty clear that bilateral VIM DBS does great a great job controlling midline tremor. Also there are some recent reports that it's effective for orthostatic tremor, which is a tremor that occurs primarily in elderly patients. They start tremoring when they stand and walk. So adverse outcomes include cognitive behavioral deterioration. We talked about that. A recent study that was published by one of the groups that is spearheading this research out of Gainesville, Florida. They have been promoting GPI as an alternative to some extent. But they just published some data looking at STN surgery that showed that if the lead is well placed in the dorsal lateral part of the STN, which is where the motor strip is-- the homunculus of the brain is represented in these smaller structures. If you place that lead in the right location, it seems to not affect verbal fluency as much as if the wire is slightly ventral or slightly dorsal. So other issues that can occur. Intracerebral hemorrhage it is the main concern. At our center, we believe our bleed rate is about half of 1%. And part of the reason we think our hemorrhage rate is so low now is because we take great care to manage our entry point and avoid high risk structures. This is all during the planning phase of the surgery, before the patient comes the operating room. Doctor Patel and I are working on trying to find the safest trajectory to the target. And by avoiding the ventricle, avoiding the sulci, where the blood vessels are higher risk, we think we've dramatically reduced the risk of hemorrhage. Infection,

also very important to have extremely good surgical technique and to instruct the patients to leave these wounds alone. We did have one infection that required removal of the entire system. We've seen several more infections from other centers over time. So that's something that can be avoided, I believe. But even at our center, out of about 150 patients, we've only had one lead infection that required complete removal. So the risk for that is pretty low, too. So I think I need to go ahead and let Doctor Patel move on to the next part as I've run out of time. And if I have time at the end, I'll come back and make some more comments. DR ANANT PATEL: Morning. I'm Dr. Patel. I'll try to make my talk really concise since Dr. Izor's alluded to a lot of the points I was going to say anyway. So not to make anything redundant and give Dr. Whitmer a little more time on the research aspects of it. So in terms of when we talk about surgery, there's some parameters that we're looking at. One, you have to choose the platform that you want to introduce your leads-- a stereotactic platform, whether it's a frame or frameless. It really depends on the surgeon's preference for that. The second issue is in the planning stage, the targeting, the imaging, the stereotactic planning, and also using the MERs to try to get to your leads in the most [INAUDIBLE] that you can. And then finally, putting the pulse generator. So DBS is done in stages. And in terms of just talking about surgical approaches, there are two systems out there-- framed versus frameless. In the framed arena there's CRW's Leksell frames. In the frameless, there's NexFrame and the STarFix. Now this is an example of a framed structure. It's a huge-- it's a large contraption. It's heavy. It's titanium. The screws are bolted, two in the front, two in the back, to support the frame. And one thing is the frame has to be locked to the bed-- just the sheer weight of that frame. And to a certain extent, when the frames are put in, these patients have to be sedated in order for them to even have this frame on and then go to the MRI. So to a certain extent, you could lose a little bit of your exam because you do have to give them a little sedation. But hopefully the exams do come back when you absolutely have to put the leads in. This is an example for NexFrame. It's frameless. This is the platform I have shown preference on. And this is another company called STarFix. There's a basic difference between the two. They both are frameless. They both use fiducials. But there are certain differences between the two. The STarFix requires you placing the fiducials on the scalp, into the bone, almost four or five days prior to surgery. You have to preplan your trajectories. You have to preplan everything. The data is then uploaded the company and they actually mold this unit. The advantage is that it saves you a lot of steps. The trajectory's already pre-calculated. And it makes your surgery quicker. The disadvantage is that if anything happens to one of the screws, you have to bag the surgery. You cannot do anything with it. Or if you decide to make radical changes in the way you're going to target, then you really have to cancel the surgery. So other arguments that folks used to make is frame is more accurate than frameless. I'm not sure that's entirely [INAUDIBLE]. There's enough data now published that the accuracy amongst any of the systems is very acceptable-- from Leksells to CRWs to NexFrame. STarFix claims that their accuracy is even tighter than the other systems out there. I'm not sure that's entirely true, but that's the data that was published. Now there are certainly advantages and disadvantages to framed versus frameless. It comes down to the surgeon's preference. I prefer frameless. There are some advantages to a frame. And the biggest advantage to a frame is if you are planning on putting multiple leads on one side, it's easier to do it on the frame than the frameless. And so I'm just going to talk to you about using the frameless approach. Surgery's done in three stages. [INAUDIBLE] Fiducial markers, [INAUDIBLE] accuracy. [INAUDIBLE] not a fixed system. Then the second stage is actually putting the macroelectrodes in. And finally, the DBS pulse generator. So putting the fiducials, it doesn't take much time. It takes about, maybe, 20 minutes. The skin is anesthetized with marking. Just make a little stab incision and put five screws, two in the front, three along the posterior vertex. You can actually get away with four screws, but we prefer five screws to tighten your accuracy. And then the next day, you do the targeting. You do the planning. And this is, I think, the most important aspect of surgery. It's the actual stereotactic planning. Use high resolution MRs. And also use and navigation software whether you're going to use BrainLAB, Stryker, or even Stealth navigation. They all have their navigation platforms for DBS. And the second portion of the surgery involves using MERs to tighten and let you place these electrodes very accurately. So in terms of targeting, you can do indirect targeting and direct targeting. And the difference is with direct targeting, you need very good MR imaging. This is an example of a 7-tesla. We have a 7-tesla. But you can make out the STN This is red nucleus. You can see the GPE, the GPI. This is the STN right here. This structure, right here, is the STN. And this is the substantia nigra. Just looking at these images, you can get pretty good at placing those. So imaging does make a difference. Unfortunately, most centers anywhere around here use 1.5-teslas. This is another article that was recently published in 2010 in Journal of Neurosurgery where they looked at different gradients, at different telsas. This is a 1.5-tesla magnet. And you can see, it's kind of blurry. You have to use [INAUDIBLE] algorithms [INAUDIBLE] try to identify where the STN is. This is a 3T tesla. And you can see the STN here. And this is much better defined with the 7-tesla. So the indirect targeting involves using what standard coordinates are. There's enough data out there that will get you into the ballpark where the STN is-- 12, minus 3, minus 5 or 12, minus 4, minus 4. Once you get to that ballpark, then you're using stimulation to try to figure out if you're too lateral, too medial, too anterior, too posterior. And that's where you start making multiple passes to try to get the optimal position. Others argue that they want to make those passes to really identify the entire structure of the STN, to really get the borders of the STN. Again, this is an example of an MER, what we look for. Once you're closer to the zona, you'll see a few noise vibrations here. As soon as you enter the STN, this amplitude really increases and you have a lot of activity. As you leave-- this is the STN. As you leave the STN, it becomes silent. And then as you enter substantia nigra, you see this rhythmic, 60-hertz frequency sound that comes out. And this is an example of an STN MER pass that you're looking for. So again, target sites. Dr. Izor alluded to what sites are used. For STN, there's a choice between-- sorry. For Parkinson's it's STN. And GPI can also be used for Parkinson's patients. For GPI, it's for Parkinson's and dystonia. And for essential tremor, we use the thalamus, VIM. So this is an example of animated lead placement for STN. There's the microelectrode going in. You start hearing some thalamic activity. This is the tip coming down. It becomes a little silent in the zona. This is the STN. Tips here. You start seeing an increase in the base. And the activities will start increasing. It becomes silent. And then you are entering the SNr, that rhythmic 60 second hertz. The microelectrode is removed. And the macroelectrode is placed. But before we remove the microelectrode [INAUDIBLE] do intraoperative testing to make sure that we do get therapeutic benefits without seeing any major stimulation-based side effects. Once we are pleased with that pass, then we'll put the actual macroelectrode in and do the testing again. We'll look for stimulation-induced side effects and also look for therapeutic benefits. If, at that time, you do get therapeutic benefits, but you are seeing a lot of stimulation-based side effects, we will not take that pass. We'll make the adjustments depending on what kind of side effects we've seen. This is an intraoperative video. Just basically our patients are kept awake. We don't use this cervical collar any more. This was of a first case we did in 2004, 2005. Again, those are the fiducial markers that's on the scalp. Skin is and anesthetized with lidocaine. Patients are kept awake. [BEEPING SOUND] DR ANANT PATEL: There's one thing the patients don't like. It's the high pitched sound. It lasts about 45 seconds. End up doing it on both sides, maybe less than two minutes. Putting the cap. Putting the frame on. Putting the reference star onto the frame. And the screws are then registered. This is the camera that looks at the reference star. Again, the accuracy is pretty good. And the next spot involves lining the entry point to the target. It's like playing Nintendo, getting that dot into the circle. Once you are within-- once the two dots are together, that's your trajectory. Then you introduce the cannula. And then, listening to the MERs now. When you're happy with it, this is the final electrode. That's placed. And then you put the final cap on it. So in summary, DBS really is beneficial for a lot these patients. Especially with Parkinson's and essential tremor, we're seeing good results even with dystonia patients. With any kind of therapy, there are risk factors in anything we do. And the biggest risk factor for surgery, as Dr. Izor had mentioned, hemorrhage and infection. We try to do everything to minimize the risk of hemorrhage by really looking at the trajectory, making sure that our trajectory is not going through a sulcus, not really going through any nearby vessels. And there's also simulation-based side effects. And that's where intraoperative testing makes a huge difference. You want to try to make sure that your placement is in a good position, that you don't see stimulation-based side effects. Because it'll be a hard challenge for the neurologist to work around those side effects. And revisions will eventually happen. Thank you. DR. DIANE WHITMER: I'm just going to tell you briefly about some research into cognitive aspects of Parkinson's disease. And it relates to some research projects that we are doing here in Austin through the NeuroTexas Institute. So as Dr. Izor and Patel alluded to, Parkinson's disease is not merely a movement disorder. It also involves cognitive and affective or emotional symptoms. There isn't a clear definition right now for mild cognitive impairment in Parkinson's disease. But recently, the Movement Disorder Society put together a task force to try to better define this and to perform a meta-analysis of the literature. And there were some really interesting results. They found that Parkinson's disease with mild cognitive impairment, PDMCI, is much more prevalent than people had previously realized. So it's approximately a quarter of Parkinson's patients have MCI. And that's a meta-analysis from

several other studies where it ranged from 20% to 40%. It's a risk factor for the development of full-blown dementia, which as you know, has a tremendous impact on quality of life. And patients with PDMCI progressed to dementia over a short period of time. Finally, there's a lot of heterogeneity in the types of cognitive impairments and the numbers of domains of cognition that are affected. So what do I mean by domains? People usually talk about five domains of cognition. Executive function, these are cognitive abilities that control and regulate other behaviors, so things like decision making, switching between rules, what people think of as very high level cognitive function. Then attention and working memory are sometimes classified as executive function, sometimes not. Memory, visuospatial abilities, and language abilities. And so in Parkinson's-- why did that get louder? In Parkinson's disease-- whoops-- patients have demonstrated deficits in each of these areas in different studies. Is there something I need to do? OK. OK. So it makes sense that patients with Parkinson's would have-- Can I help? No? OK. Would have some cognitive impairment given that the same brain structures that are involved in movement, in other words, at the basal ganglia , structures like subthalamic nucleus, the globus pallidus. These are part of motor circuits, but they also have connections with frontal cortex. And these same structures are part of associative circuits as well as having connections to the limbic system. And so they're involved in emotion as well. And this has been shown by anatomy, physiology. This is known for a long time. And so you can actually see here that there are different regions of the subthalamic nucleus that are part of these very different functional circuits. And this touches upon why getting accurate lead placement for the stimulation therapy is important. Both Dr. Izor and Dr. Patel already addressed the fact that subthalamic nucleus deep brain stimulation is a very effective treatment for the motor symptoms of movement disorders. And this has been shown in several very large clinical trials. However, it's actually controversial whether deep brain stimulation makes cognition better or worse or whether it has no effect at all. So here's a set of studies that showed that subthalamic nucleus DBS improved cognitive performance. There's an example of a random number generation task, cognitive flexibility, reaction time, specific to visual memory, even some improvement in object naming. Conversely, there's a set of studies have shown adverse effect on cognition including things like object naming. And finally, there's a set of studies that have suggested, look, there's no effect. When you control for all these other factors-- the surgery itself and the progressive nature of the disease over time-- the actual stimulation itself, on a very large population, comparing means between groups, does not adversely affect cognition. So it's a very difficult issue to try to get to the bottom of. And why is it so difficult? The patients are very heterogeneous. Some studies are very small numbers and case reports. Some studies don't have adequate controls. You need a new the patient group that you can compare surgery to who has the same set of symptoms and is progressing at the same rate. And that's very hard to accomplish. So these problems are not insurmountable, but we need very large clinical trials where patients are tracked longitudinally. And we need disease-matched controls as well as age-matched healthy subjects. And those clinical trials are also complementary with studies on smaller numbers of patients where we can actually measure from the brain at the same time that we're measuring cognition and behavior. And that's the research approach that we're taking. So a lot of these studies use neuropsychological testing, which provides a very gross view of the brain. You can measure what very large brain areas and multiple systems are doing together. The positive side is that these are clinically validated. They've been compared to healthy people and tested on very large populations. But some of these tests that were developed 50 years ago are a little outdated. For example, the Wisconsin Card Sorting Test for executive function mixes together working memory, and rule changing, and matching. There's also functional MRI. And that's where we get imaging of the blood flow in the brain at the same time that someone performs a computerized cognitive behavioral task. Those are use investigationally, not diagnostically. And those are great for high spatial resolution of specific brain areas that are involved. But there's poor temporal resolution. In order to get accurate fMRI imaging, you need to average the brain's activity over several minutes. And it's also very challenging, specifically with patients who have movement disorders, to get clear images of their brain because they suffer from dyskenisias and tremors. And that all introduces artifact in the brain image. And yet, if you anesthetize them to get rid of those motion artifacts, then they are not awake to participate in cognitive behavioral testing. So the approach that we look to is using electrophysiology. And I just want to mention, all of these approaches are complementary. I think we need all of them. With electrophysiology, we can measure the electrical activity of the brain during computerized cognitive behavioral testing. And because in the case of DBS surgery-- Dr. Izor and Patel alluded to this, but I'm not sure if they made explicit-- patients are awake. And they're participating. And they're interactive. And that's so, for clinical reasons, to get optimal placement of the lead with optimal benefit and minimal adverse effects. And that gives us a window of opportunity to measure what the brain is doing while patients are performing a very specific, carefully well-controlled cognitive task. For example, involving rule switching. I don't think I have time to go into detail on this, but I just wanted to mention there are very different spatial scales from which you can measure the electrical activity of the brain. So for getting the lead in the appropriate place, single units. So outputs of individual neurons is what we measure, and listen to, and watch. From the DBS lead itself, you can measure the average electrical activity over, say, 10,000 neurons acting in concert. It's sort of like trying to interpret what's happening in a football game from hearing the roar of the crowd rather than from trying to listen in onto an individual conversation. So this is an approach that we're taking here, simultaneous measurement of brain signals while patients are awake and perform cognitive behavioral testing. I don't have time to explain the math behind how we analyze our data, but I'll just mention that we make these time frequency spectrograms. And the color tells us how much power there is of a certain oscillatory component. So any electrical signal can be broken down into a sum of sinusoids, a set of oscillations all added together. And in this case-- this was an electrode over motor cortex. Every time a patient moved-- and this example, it was an epilepsy patient. There was a decrease in its power in this band, and a simultaneous increase in these faster signals. Where we'd like to go with this is also being able to stimulate-- so what I talked about so far was that our research study is measuring from the brain while people participate in cognition. We also have the technology to do this with DBS turned on. And if any of you have a background in electrical engineering, you may know that's a very challenging thing to do because the stimulation itself can swamp the signals that you're trying to measure. But there is a technical solution to that. And so now we have the ability to determine, not only what is the subthalamic nucleus doing when someone is trying to perform a specific task, like learning a new rule, but what effect does subthalamic nucleus DBS have on the brain signals at the same time that it may affect performance. So I'm going to wrap up there just because we're out of time and open it up for questions. And I'd like to thank the organizers of this event as well as Dr. Izor and Patel for collaborating in research. And then, if you let us know to whom the question is addressed, all three of us can answer any questions. Thank you. AUDIENCE MEMBER 1: My question I have for you, do you have a chance to do the local field potential after you've inserted the lead, before and after the stimulation. Can you do that? DR. DIANE WHITMER: OK. So the question for the people that are watching by video-- I have to repeat it-- is do we have the opportunity to-- AUDIENCE MEMBER 1: So after Dr. Robert, Dr. Izor, and Dr. Patel implant the lead, you do measurements of the local field potential. DR. DIANE WHITMER: Correct. AUDIENCE MEMBER 1: Can you do the local field potential before with the cognitive function testing? Do the cognitive function testing before and after the stimulation? DR. DIANE WHITMER: So the question is can we measure cognitive function and electrical signals from the subthalamic nucleus before and after stimulation? AUDIENCE MEMBER 1: Yes. Can you do that? DR ANANT PATEL: Yes. That's possible. AUDIENCE MEMBER 1: Because before you answer, this is my thought. This is a very interesting study that you're designing. Excellent study. But the question is this. We know from animal studies that immediately a stimulation can actually decrease or increase the level of dopamine discharge. And any cognitive function that you perform does rely on a good attention. Now all these patients that are on the table for the surgery awake, they're off medication so we know that their attention span is going to be poorer because of the lack of the dopamine. Now in DBS surgery, location is location and the best outcome of the surgery is based on the best location. We know from animal studies that if you have a wrong location of the lead, you might decrease or increase the dopamine discharge. So-- DR ANANT PATEL: How will we address-- AUDIENCE MEMBER 1: So I give the whole speech because here is my point, first you need to have a good location of the lead to know where you are. Because you might actually, by performing your test and seeing the [INAUDIBLE] of the STN you could theoretically make it worse than it is in reality if the lead is too ventrally. And you actually diminish the release of the dopamine as you stimulate. Because you measure the local potentials with the stimulation. And important is that you want to prove that you have a good benefit of the stimulation that relies on a good dopamine discharge that you, presumably, you discharged when the lead is in the right place. DR. DIANE WHITMER: So is there a question? I didn't really hear you for the-- AUDIENCE MEMBER 1: So the question is, at the same time, that maybe that you think this is good for your design, for your study, would be good for you to measure the local field potential after the lead is implanted before and after the stimulation. DR. DIANE WHITMER: Mhm. AUDIENCE MEMBER 1: Because then you can

see actually if you create the dopamine discharge theoretically by placing the lead in the right place and improving the cognitive function. DR. DIANE WHITMER: OK. AUDIENCE MEMBER 1: You are going to perform a test there in the surgery. DR. DIANE WHITMER: So I think the point, for people remotely, was raised that simulation itself can affect local levels of dopamine, acutely. And there is a very complicated relationship that I didn't address in my talk between levels of dopamine and cognitive performance. There's a whole set of studies that precede DBS that just relate dosages of Levodopa therapy to cognitive outcomes in these diseases. So the dopamine story is definitely another complication. And it's another variable. And I think the study that we're doing presently, we're not stimulating. We're taking passive recordings. The first question is, is the subthalamic nucleus playing a role in a specific type of cognition that we know was suggested by animal studies, which hasn't yet been shown by humans. Now where we were going to go was the simultaneous stimulation and measuring. But I think it's also a good idea to look at-- just like the work of Dr. Bronte-Stewart. She wasn't studying steady relationship is measuring effects on the local field potential signal before and after simulation. And to make that comparison, I think that's a great idea. AUDIENCE MEMBER 1: And I think the location of the lead is absolutely important. Because any paper about DBS is going to ask precisely where is the lead. DR. DIANE WHITMER: Right. So the way-- AUDIENCE MEMBER 1: In fact, it's [INAUDIBLE]. DR. DIANE WHITMER: So we're addressing lead location in a couple ways. One is through microelectrode recording that Dr. Izor in collaboration with Dr. Patel. So we're mapping out the boundaries of the STN. And the other thing we do is post-operative neuroimaging in our research patients to confirm lead placement. So we have anatomy, physiology. And we have some imaging. And so that's how we're trying to address this. DR. ROBERT IZOR: And just another comment, I think we're just trying to develop a new modality of recording data that we can use for many different things. And eventually it might be possible that these patients when we see them in the clinic, we're able to collect that data-- obviously this would require collaboration with Medtronic. But at some point, it may be possible to distinguish which patients have lead placement that is suboptimal. Where is that? Versus patients who are optimally placed. And collect data both before and after stimulation. And then that gives us more objective data to use just as they're looking to answer these same questions. Why do some patients have cognitive issues and some not depending on where the lead is placed? AUDIENCE MEMBER 2: And this is-- AUDIENCE MEMBER 3: Just quickly, when you're monitoring the frequencies and everything, what are the parameters that you are changing? Increase stimulation, increase amount, and so on. DR. DIANE WHITMER: That's a great question. DR. ROBERT IZOR: So the question is what parameters are we able to modify with the DBS on a given patient. The lead has four contacts, so we're able to choose which contact we're going to create as a negative versus a positive charge. And then, the pulse generator, which is like a pacemaker battery implant, we can program that to adjust voltage, pulse width, and frequency. There's some limitation on how far we can go-- the strength of the battery, a lot of things. But there's a lot of adjustability there that you just don't have with the thalamotomies and pallidotomies. So there's a lot of adjustment. Even in a lead that isn't optimally placed, you can usually find settings that provide noticeable and appreciated benefit. But a recent study that was just was published recently shows that if the lead is in the best location, that those patients really do better over the years than the ones that have leads that are maybe even a millimeter or two millimeters away from the ideal target. And you can't program around that. AUDIENCE MEMBER 3: OK. AUDIENCE MEMBER 4: How do account for the fact that deep brain stimulation seems to accomplish the same thing as ablation [INAUDIBLE]. Pallidotomies, or destruction of the nucleus, you get the same effect with stimulation as you do with destruction. DR. DIANE WHITMER: So the question was-- are you asking about clinically or in research? So the question was-- AUDIENCE MEMBER 4: Clinically. You ablate the nucleus, you get improvement. You stimulate the nucleus, you get improvement. I would think it would be the opposite effects. DR. ROBERT IZOR: Well-- DR. DIANE WHITMER: Can you repeat the question? DR. ROBERT IZOR: Yeah. For the remote location, he's asking why do we see similar benefits comparing ablation to stimulation, ablation being burning a hole in the target. And in the case of the STN, the nucleus, when you have Parkinson's disease, is overreactive. It is producing more data, sending that to the globus pallidus internus. And when you burn a hole in that location, you're turning down that data figuratively speaking. And that improves the expression of the disease-- tremor, rigidity. You can't really adjust it well though. Now with stimulation, you can also turn up simulation high enough to really disable the neurons and the data coming from that. But more importantly, you can modulate what's coming out of it. You can change the frequency, and the energy output, and the signaling that goes to the globus pallidus. So I think you have more adjustability with DBS not just because but you're turning down the output in the STN, but you're actually modulating what's coming out of it. Now in the VIM, when we're listening, for example, with an MER, you hear tremor cells quite often in the patients with severe tremor. And by using simulation, similarly, you're probably reducing the output of data from that area just the same as burning a hole would but with more adjustability. OK. [INAUDIBLE] AUDIENCE MEMBER 4: OK. AUDIENCE MEMBER 5: Sir, I have a question, if I may. The leads that exit from the skull, how do you track them down to get their actual stimulator? DR ANANT PATEL: The question is how do you get the leads down from the scalp incision to the pulse generator. What we do is we have a toning device. This is a tubular structure. It's the same system that we use for shunting. And what you do is you-- sorry. So what you do is-- it's a tunnel. You're passing this hollow tunnel from the site of the battery all the way to the scalp. And them through that tunnel, the cables are put in. And you pull the cables up to the scalp. Then you connect the two ends. DR. DIANE WHITMER: Were you asking from the battery to the lead? AUDIENCE MEMBER 5: Yeah. Yeah. Pretty much. Because it seems like there are quite a lot of structures that you have to traverse with that tunneller. DR ANANT PATEL: Right. AUDIENCE MEMBER 5: I mean, is it a [INAUDIBLE] procedure to do? DR ANANT PATEL: No, it's not. Because the wires are really in the subcutaneous tissue. It's really just under the skin. AUDIENCE MEMBER 5: OK. DR ANANT PATEL: Then there aren't any critical structure out there. But if you go really deep into the neck area, then your carotid's there, [INAUDIBLE] jugular. Then you get into trouble. But typically the tunnel stays under the skin. Thank you very much. AUDIENCE MEMBER 6: By the way, it was an excellent and fascinating talk. Pretty heavy stuff. Excuse the pun. I'm sure you guys aren't really frightened about the incursion of midlevels onto your territory. But who knows? Apparently Phoenix University is offering a six-month course on DBS. It's coming online pretty soon. And they're in negotiations with Walmart. [LAUGHTER] AUDIENCE MEMBER 6: There are going to be some DBS centers at most Walmarts throughout the country pretty shortly. [LAUGHTER] AUDIENCE MEMBER 6: Thanks for a great talk. AUDIENCE MEMBER 7: You know there's a saying, you put a hammer in somebody's hand, everything looks like a nail. AUDIENCE MEMBER 6: Of course. AUDIENCE MEMBER 7: And that's the problem. If I may answer to your question-- nobody knows the mechanism of deep brain stimulator. But the bottom line is, it's not about changing the frequency of these charges. It's about changing the pattern of firing. And by stimulating, you actually disrupt that burst of activity that actually impairs [INAUDIBLE] thalamal striatal projections to moderate your motor behavior in response of what's going on outside. Having a circuit-- because in [INAUDIBLE] you talk about circuits. Having a circuit, like in Parkinson's disease where the neurons, because of pathological changes, are starting to fire independently. And they do whatever they want. They don't allow the cortex to moderate the subcortical levels based on input from outside. And what you do by stimulation, you actually disrupt that [INAUDIBLE] pattern of fragments [INAUDIBLE]. That's what you do. AUDIENCE MEMBER 8: I had a quick question. DR. DIANE WHITMER: Yeah. AUDIENCE MEMBER 8: After DBS-- thanks. After DBS placement, how long do you usually have a positive effect? You know when we start on Sinemet, for example, it has a really great effect in the beginning. And then eventually you start to get more off times and side effects. How about with DBS? DR. DIANE WHITMER: Yeah. I should let a neurologist answer that. We'll let Dr. Izor answer that. But from what I've seen from collaborating with neurologists-- so at Stanford Movement Disorders, there were some patients 10 years out. They just needed to get their battery replaced. But DBS was helping their symptoms 10 years later. AUDIENCE MEMBER 8: And there's no decrease in their efficacy or anything? DR. DIANE WHITMER: Well, deep brain stimulation is not a cure for the disease. And it's a controversy. It's unknown, right now, whether it can have a protective mechanism. So people will still progressively decline. We don't know whether they're declining more slowly than if they didn't have deep brain stimulation. But it really is just treating the symptoms. DR. ROBERT IZOR: Well, I would-- DR. DIANE WHITMER: Would you like to add to that? DR. ROBERT IZOR: I would beg to differ a little. There is data. It doesn't express the mechanism of how it might be protective. But there's data that shows that the people who have the surgery earlier in the course of the disease, they do better. And it can't be just attributed to therapeutic benefit. So it doesn't stop the progression of the disease. But there is potential there that it may do something. If you look at the anatomy of where we are, we're literally a millimeter or two away from substantia nigra, which is where we see the dramatic loss of dopaminergic neurons. Now that's not the only thing that happens in Parkinson's disease. But that's what causes the greatest motor disability. Also other areas are nearby. The neurogenergic system is nearby. And in some of the animal models and the rat models, they're simulating in the brain. And they're finding that brain-derived neurotrophic growth factor is going up

three times in that area. And if you remember what I was saying earlier, we all try to figure out how to get growth factors into the brain. Exercise does it, but nobody in America wants to exercise anymore. And DBS apparently, in rats anyway. So there's another avenue of research. I think there'll be some more surprises. AUDIENCE MEMBER 8: So from a clinical perspective, if treating earlier on with DBS has better efficacy-- if I can use that word. Then what, clinically, what indication should we say, OK. Now it's time to refer you to DBS as opposed to continuing on medication. DR. ROBERT IZOR: So just to say the question again, she wants to know what are the criteria. What makes a good candidate for surgery? I think the most important thing is how well is the patient doing on medication. And if they're doing really well on medication, they're not having any adverse effects, and they're able to do everything that they want to do-- not what you perceive them able to do. Because I often have patients that come in. They have a little bit of tremor, a little rigidity in their left arm. They're right-handed. So, you know, it's hard to convince someone like that to go for surgery. But if it's their right hand with the same level of disability, they're not able to write. They're not able to do a great many things as well as they used to. And the medication is not adequately controlling that, be it tremor or just even fine motor control. As long as we're seeing 30% or more difference in on versus off state, they will probably do better with DBS. And so I'm offering it earlier and earlier. The contraindications, though, are important. If the patient hasn't had Parkinson's for more than five years-- sometimes multiple system atrophy, psychiatric conditions, can sometimes mimic Parkinson's disease. And if you do surgery on patients with MSA, they may not work. If it's not for tremor, for example. Their gait may continue to decline. So you want to be a little bit careful when you do it. Also the elderly, people over the age of 80, they have multiple morbidities. You want to be careful. But that's not an absolute contraindication either. And then the next big one is dementia. If they have substantial dementia, you have to be very reluctant. I have patients with dementia that we've done surgery on that got tremendous benefit from DBS. I've had other patients with dementia that we'd offered the surgery that became worse within a year. And one case died. But the vast majority of the time, it does not seem to impact cognition sufficiently for the patient or family members to notice. So I hope that answers it. AUDIENCE MEMBER 8: If I could ask one more question, is there any difference. Is there more benefit in early-onset Parkinson's than, say, what we usually see age-wise? DR. ROBERT IZOR: So she wants to know is there more benefit in early-onset patients. And I would say, yes. Early-onset patients tend to have more dystonia. They tend to, more often, be tremor dominant. And medications just aren't that good at controlling dystonia or tremor, whereas DBS is the only hope. And quite often, it's spectacular. DR. DIANE WHITMER: Thank you. DR ANANT PATEL: Thank you. [APPLAUSE]