



MEET THE SCIENTIST WEBINAR OCTOBER 2019

Deep Brain Stimulation for Treatment-Resistant Depression: A Progress Report

Presented by: Helen S. Mayberg, M.D.
Moderated by: Jeffrey Borenstein, M.D.

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- Dr Borenstein: Good afternoon, and welcome to the Brain and Behavior Research Foundation's Meet the Scientist Monthly Webinar Series. I'm Dr. Jeff Borenstein, President and CEO of the Foundation, and your host for today's webinar. This afternoon, Dr. Helen Mayberg will present Deep Brain Stimulation for Treatment-Resistant Depression: A Progress Report.
- Dr Borenstein: The Brain and Behavior Research Foundation funds the most innovative ideas in neuroscience and psychiatry, to better understand the causes, and develop new ways to treat brain and behavior disorders. These disorders include: addiction, ADHD, anxiety, autism, bipolar disorder, borderline personality disorder, depression, eating disorders, OCD, post-traumatic stress, and schizophrenia.
- Dr Borenstein: Since 1987, the Foundation has awarded more than \$408 million to fund more than 5,900 grants to scientists around the world. 100% of every dollar donated to research goes to research.
- Dr Borenstein: I'm delighted to introduce Dr. Helen Mayberg. Dr. Mayberg is the Director of the Center of Advanced Circuit Therapeutics at the Icahn School of Medicine at Mount Sinai. She's a member of DBRF's Scientific Council, was a 2002 Distinguished Investigator Grantee, a 1995 Independent Investigator Grantee, and a 1991 Young Investigator Grantee. She also received the Foundation's 2007 Falcone Prize for Outstanding Achievement in Affective Disorders Research.
- Dr Borenstein: Today's webinar will begin with Dr. Mayberg's presentation. This will be followed by a question and answer period. To submit your questions, please use the Questions tab on the control panel on your screen. Feel free to submit your questions at any time. Following the presentation, I'll ask as many as possible in the time allotted.
- Dr Borenstein: Now, I'm pleased to introduce Dr. Mayberg. Helen, the floor is yours.
- Dr Mayberg: Thank you very much, Jeff. It's really a pleasure to be with you, and to be with the audience. It is an unusual situation to be talking to yourself to many people from the office, but it's really a fantastic opportunity.

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- Dr Mayberg: I want to get it to actually be at the beginning of my talk, and [inaudible 00:03:02] end of my talk. Just give me one second, and we will get started. There we go.
- Dr Mayberg: What I'd like to do today is to really review the last five years, mostly, of what we've been doing with Deep Brain Stimulation for treatment-resistant depression. The reason I frame it as a five-year progress report is it was five years ago that I gave my first webinar on this topic, which really summarized the first ten years of our work.
- Dr Mayberg: I first want to make a few disclosures. I'm going to be discussing an experimental treatment for depression, and the off-label use of devices that are implanted in the brain. There is an actual property associated with this work, which has been licensed to Abbott Laboratories, and we'll talk a little bit about the clinical trial that St. Jude Medical, the previous company, ran.
- Dr Mayberg: I also want to have everyone be aware that actually the Distinguished Investigator Award that I had from DBRF and NARSAD in 2002 actually funded the original pilot studies of this work. I'm extremely grateful to the organization, to the donors, and their investment in this project. Because without them, none of this would have happened.
- Dr Mayberg: I want to have this presentation really highlight the work of my team at Emory. This work, over the last 13 years at Emory, has really been fundamental to all of the information that I'll convey today. What becomes very important to realize about research of this type is the breadth of experts that are required to participate.
- Dr Mayberg: As you can see from this slide, it's so dependent on the choreography between psychiatry, neurosurgery, to have a psychotherapist, to have good clinical coordinators, but importantly, to have a broad collection of imaging, electrophysiology, and engineers. I've really been fortunate to have just a fantastic team to work on this project. I'll give them shoutouts throughout the presentation.
- Dr Mayberg: I want to start with actually framing something that many of you may not appreciate, and that most scientists in the audience actually take for granted. I think as we enter 2020, we almost have a new axiom as we think about psychiatric disorders broadly. Depression is really an exemplar.
- Dr Mayberg: But that we really talk about these brain diseases as circuitopathies, meaning there are an organized abnormality of brain regions, and that there is failure of the way these brain regions interact with each other. That the organization of brain regions mediates different behaviors, and their dysfunction mediates the syndromes as we've come to understand them.
- Dr Mayberg: As one looks at this slide with movement disorders like Parkinson's, or obsessive-compulsive disorder, pain, addiction, we actually realize that if one can organize an illness

into this kind of brain organization, you have a foundational structure for imagining treatment with neuromodulation such as Deep Brain Stimulation.

- Dr Mayberg: What, exactly, are we talking about when we use the term "focal modulation of disease circuits?" Whether or not one is thinking about a non-invasive intervention, like Transcranial Magnetic Stimulation, or as I'll talk about in the next hour, Deep Brain Stimulation, or the invasive implant of an electrode in the brain, where it stays basically indefinitely, we need to actually fundamentally understand or plan certain things, if this is something we want to do for a particular group of patients.
- Dr Mayberg: First, we have to decide why do we want to do this? Need is critical. The second obvious questions is where are you going to put this wire? Where do you want to stimulate?
- Dr Mayberg: The third is what should happen? Are we trying to increase the brain activity? Decrease the brain activity? Pace it? Interfere with it? We need to actually decide what that should be, because that will mechanistically help us to know what to do.
- Dr Mayberg: We need to have some rules as to who should be eligible. Do we have some kind of inclusion criteria? Is there some biomarker that might help us to know who is suitable for this particular intervention? This is true whether it's invasive neuromodulation, or it's who gets therapy, and who gets a medication.
- Dr Mayberg: Lastly, we need to have some idea about how we're going to stimulate. Are we going to turn it on only on demand? Is it going to be intermittent? Is it going to be continuous? Or is there going to be some trigger that we can use that will set off the stimulation to occur, perhaps temporarily?
- Dr Mayberg: At the end of the day, our goal is how do we match a target in the brain to either the disease, the symptom, and importantly, the individual patient, so that we can actually devise personalized algorithms to optimize treatment response for a given person?
- Dr Mayberg: What is DBS? Again, many people are familiar with this, so this is a crash course. You basically have an electrode. You can see how small it is. Here it is blown up. And at its tip is about a centimeter at the end that has four individual contacts in this space, which allows you, when implanted, to hook it up to a battery pack and deliver current to one of these four locations or all of them. So that one can deliver minute amounts of current at different frequencies, and at different amplitudes, to the brain in the area designated.
- Dr Mayberg: How do we get it to where we want it to be? Well, in the operating room, there are sophisticated surgical planning stations now, where you can drive this small wire to a very precise location anywhere in the brain, with high accuracy and precision. This stereotactic guidance is what's made this kind of technology possible.

- Dr Mayberg: A patient is implanted awake. They're centered and stabilized in a frame that allows the neurosurgeon, under this stereotactic guidance, to actually put the electrode to the precise place in the brain that they choose. Then, once implanted, the electrode can be hooked up to a connector cable that actually then can communicate with a pulse generator. Basically, a battery pack that's implanted under the skin in the chest, and can deliver the current to the location in the brain as required.
- Dr Mayberg: Now that we know what we want to do generally, and we know what we're going to do surgically, specifically, let's go back to think about what were we thinking in 2001 when we decided that we might investigate the potential for Deep Brain Stimulation for intractable treatment-resistant depression?
- Dr Mayberg: We know that depression is a disorder with a number of signs and symptoms, dominated by abnormal mood, and lack of interest. We also know that there are many treatments available that, thankfully, are quite effective in most patients. The problem is getting the patient the treatment that's best for them can often be trial-and-error.
- Dr Mayberg: But most critically, about 10% of patients become treatment-resistant over time, even when they've previously responded to available interventions. If a patient reaches a point where they are failing ketamine, TMS, or particularly ECT, electroconvulsive therapy, there really are very few options.
- Dr Mayberg: Back in 2001, where ketamine was not even available yet, a rationale to use neuromodulation as a potential strategy was driven by the advances in functional neurosurgery, in imaging, particularly, and an already established body of work in Parkinson's disease. Looking backwards, it was quite naïve to think that we should think about depression like Parkinson's disease, but at the time, everything known about Parkinson's really pointed the way that this might be a strategy.
- Dr Mayberg: I think what's important now to think about as one considers why would we do Deep Brain Stimulation for treatment-resistant depression, it's beyond just not having an alternative treatment. We need to think about, if we're going into the brain, what is it that we want to change?
- Dr Mayberg: I'm always drawn to this quote from William Styron, who wrote about his own depression in *Darkness Visible*. He described it as "A gnawing agony." To describe a feeling as something painful, but a painful self-loathing, is really an uncomfortable thing to even read. For those of us that don't suffer from depression, I think we can't even imagine what that's like.
- Dr Mayberg: But what's striking about his description is the fact that it also describes just not the psychic pain, but the loss of energy and attention. To me, as a neurologist, most importantly, this sense of feeling immobilized. The idea that one is in intense pain, and one can't move.

Dr Mayberg: I think as we start to really dissect all of the symptoms that we see in depression, we can really reduce it down to intense negative mood, with the inability to put thought to action. To be in a state where you can't get away from inside yourself is really a state that none of us would want to be in. To me, we might imagine recovering as being, perhaps, just the ability to move. Or to be without pain as a primary focus. Or even the return of control over oneself.

Dr Mayberg: With that in mind, back in 2003, the first patient, we actually said, "What is our rationale? What do we want to have happen?" We had evidence from our prior work with imaging in depression, that in the state of intense negative mood, the so-called "psychic pain," and there is a Brain Area 25 seems to be overly active. In concert, areas of the brain that control thinking and action are turned off, and that with successful treatment, one can downregulate Area 25, and correct these underactive regions that control thought and action.

Dr Mayberg: What our hypothesis was was to block this overactivity, sort of block what we thought was driving the negative mood, and that that, in turn, would also change regions that were connected to Area 25, and correct the other symptoms. This was incredibly simple-minded. We knew that Deep Brain Stimulation in Parkinson's seemed to block abnormal brain function in Parkinson's, and so we thought we wanted to block the abnormally high 25, and we would then correct the rest of this circuit.

Dr Mayberg: We looked at a group of patients who had severe treatment-resistant depression. They had been ill more than four years. They had failed more than four treatments, including ECT. They had high severity scores on the Hamilton Depression Rating Scale, and we basically targeted this area that we had seen with our PET scans. We targeted that on the MRI. We used atlases to know where, precisely, it would be, and we implanted two electrodes deep in the brain, that would basically sit right at this Area 25 and the surrounding white matter.

Dr Mayberg: When we turned it on at the same settings used for Parkinson's disease, high-frequency stimulation, and we followed the Hamilton Depression Rating Scale over six months, we saw a fairly rapid change in depression scores. Actually that progressed over the course of six months, and four of the six patients showed a dramatic improvement over that timeframe.

Dr Mayberg: More importantly, or equally importantly, we saw that the overactivity in Area 25, here in red, actually was downregulated. We blocked Area 25, as well as areas connected to Area 25, and we corrected underactive areas throughout the network, throughout the cortex. We had evidence that we could safely go into the brain, we could stimulate and affect the symptoms, and change the brain activity as hypothesized.

Dr Mayberg: We were quite excited. We, in Canada, here's Dr. Lozano, the surgeon. We extended the studies from those first six patients to 20 patients. We followed them not just for six

months, but out to a year. In this first 20 patients, we again saw this fairly rapid drop in the depression scale. When it drops below 50%, as it's starting point, we consider that a response. We were seeing that, at six months, we were seeing 60% of the subjects were showing a significant improvement that was sustained out a year.

Dr Mayberg: When I moved from Toronto to Atlanta, I had a new team, lead by Paul Holtzheimer, psychiatrist, and we recruited a new group of patients. We studied those unipolar patients, as well as bipolar II patients. We implanted them similarly to how we had done in Toronto. We didn't turn anything on for the first month, so we did a sham first month on the study, and then turned the patients on after a month, and followed them again for six months.

Dr Mayberg: What we found is we also saw a significant improvement. We didn't do quite as well as we had done in Toronto. But that with continued trial-and-error stimulation over two years, we could actually improve the depression ratings in 90% of the subjects. But it took more time.

Dr Mayberg: We further, in the group in Toronto, continued to follow the patients with ongoing DBS out to six years. As you can see in this paper published by psychiatrist Kennedy, who was our lead psychiatrist in Toronto, that basically a year, two years, three years, the response rate was maintained over time, and even after 42 months in the study, we had a sustained response rate that was really quite dramatic, given that these had been ECT-failing patients.

Dr Mayberg: Really, the evidence to us, whether it was in Toronto, or in Atlanta, was that if you got better, you stayed better with ongoing stimulation. This is as though you have continuous stimulation in your brain. People often may continue on their meds, may not. But that you have a continued response over time.

Dr Mayberg: This is where we were back in 2014, when I presented on the webinar like this. We were optimistic. We had new science underway. All systems were making steady progress. Then, there was evidence that the ongoing randomized clinical trial, the BROADEN study that was initiated by St. Jude Medical, looking at this area of the brain in a 15 center, 200 patient, sham-controlled, double-blind clinical trial for commercialization, was halted.

Dr Mayberg: It was halted at the halfway mark, after 90 implanted patients, when the company had been asked by the FDA to break their blind and look to see where they were for a futility analysis. Basically to see, if they did the full 200 patients, would they reach the planned difference between active and sham stimulation?

Dr Mayberg: Here's the data, at the point that that study was halted. That the red line is people that were implanted, but did not have the stimulator turned on for the first six months. The so-called "people that you'd be looking for a placebo effect." The blue line, the patients who received active stimulation in Area 25.

- Dr Mayberg: As you can see, at the six-month endpoint, not only did active not beat sham, but neither group showed much of a response. There was nearly at the projected placebo response rate, a response in both groups.
- Dr Mayberg: At six months, patients were knowledgeable that they would now, for the next six months, have active stimulation, but they didn't know what they had received for the first part of the study. As you can see, that by nine months, about 30% of the patients were better, a little improvement. But really not much more by 12 months. There wasn't a big jump in the control group when they got active stimulation, and this was quite disappointing.
- Dr Mayberg: I want to point out at this time that this was a group of patients that were 50/50 male and female, had major depressive disorder, many episodes, profoundly chronic patients, in their current episode on average over 10 years, many past treatments, many hospitalizations and past ECT. This was a profoundly ill group, and this result was quite disappointing, I think, to many people. Me included. And quite surprising based on what we had seen previously.
- Dr Mayberg: But there was another part to this story that all is contained in the paper published in Lancet Psychiatry in 2017, that because patients are implanted, the study did not end at 12 months. Just the commercialization part of the project. These patients continued to receive ongoing stimulation out to two years. What you see is, at 12 months, it was a 40% response rate, but by 18 months, it was a 51% response rate that was sustained out to two years, when the study was closed.
- Dr Mayberg: We have a conundrum. We show a progressive change over time. The only statistically identifiable factor that explained how you can go from a 20% response rate at six months, to a 50% response rate at 18 months and two years, was a contact change. Where we were stimulating on the electrode.
- Dr Mayberg: There was no verification other than the post-surgical MRI to know. There was no way to know if psychotherapy or other rehabilitative activities might have contributed to this change over time. But this is in a setting of ongoing stimulation.
- Dr Mayberg: What happened was, at the end of two years, patients that were still enrolled in the long-term followup were offered explantation, you could take the whole system out, or you could have a rechargeable battery. Half the patients, predominantly the ones that showed a response, received the rechargeable battery. 37 of them were explanted. There had been four deaths, several of them early in the course of the experiment, and there were five patients at the time I made this slide that still hadn't decided if they would get a rechargeable battery or not. Their initial battery was still working.
- Dr Mayberg: What's important to realize is that this finding is in the context of other research going on in treatment-resistant depression in other groups, looking at other targets in the brain.

There's research going on in the ventral capsule, in the ventral striatum. The ALEC, the anterior limit of the internal capsule target. This was also a randomized, sham-controlled clinical trial, done by another manufacturer. It was halted after 30 patients, because active did not beat sham stimulation, despite considerable open-label data of good responses in patients.

- Dr Mayberg: A study done in Amsterdam in this target took a different tactic. They did open-label stimulation for a year, and then showed when you blindly, so the patients didn't know, turned the stimulator off, you would lose the effect. This was a positive trial, but not for commercialization.
- Dr Mayberg: There were other studies in Area 25 showing these very similar, more than 50% of the group's response rate, but not with active versus sham. There's work on the lateral habenula. There's important work going on now with stimulation to the medial forebrain bundle, who also in a randomized, controlled trial of three months, active did not meet sham, even though open-label stimulation can be quite effective and sustained.
- Dr Mayberg: Overall, DBS for depression, at last count, publications is more than 350 people implanted. The largest number of patients is in the target I'm going to continue to talk about, in Area 25, the subcallosal cingulate.
- Dr Mayberg: But I think this fundamentally brings up the point of what are we missing here? How do we see these sustained, long-term effects, and when they're put into the active versus sham, highly-controlled situation, done in multiple centers at the same time, we're actually incredibly underwhelmed?
- Dr Mayberg: Well, I think that we need to think about the fact that there is a very binary response in the society to these kinds of results. I want to impress on all of you that the impact this has had on patients that are implanted, who can be doing well, or the scientists that are agonizing over "What are we missing?"
- Dr Mayberg: You can even see, at the media level, writing in Scientific American, basically the "Much-touted DBS treatment has failed." And the New Scientist, everyone trying to really understand and get their head wrapped around what might we do different. What are we missing? How to see it as a setback and not a terminal blow, which I think was an open-minded point-of-view.
- Dr Mayberg: I think it really tells us that, scientifically, we have to take the attitude are we optimists? Are we pessimists? Or are we scientists? I think that we have to ask, as clinicians, is any of this worth pursuing given these contradictions? I put myself in both the optimist and the physicist category, but I think at the end of the day, it's really about "follow the data."

- Dr Mayberg: What does the data tell us? That was our strategy at Emory, because the clinical trial was happening in parallel to our own ongoing work. In our group of subjects at that time, 28 patients had been implanted, we've just published on what is the eight-year long-term followup. This paper came out last week, in the American Journal of Psychiatry.
- Dr Mayberg: This characterizes this cohort that we've followed very closely over eight years. We actually have data out to 11 years, but reported on eight. Actually, what we see is a sustained effect with ongoing stimulation, and here, showing the response and remission rates, that again, if you get better, you stay better.
- Dr Mayberg: We can demonstrate that if you are well, and you're getting active stimulation, and your depression rating has gone down, and you have a blind discontinuation, you'll get sick over several weeks. If you turn it on again, the depression, again, goes away. We've even seen that over years, that patients can come in with a broken device, or their battery fails and needs to be replaced, you can have a spike in the depression score, and as soon as you replace the batteries, the depression is again treated. So that these are not controlled studies, we're very open about what we know and what we don't know, but it is dramatic to see patients who have been this sick basically convert to being euthymic, being active, and with ongoing stimulation, get on with their lives.
- Dr Mayberg: How do we reconcile all of this? I think, again, if you take a scientific approach, you really try to need to understand what's going on in responders relative to non-responders. We're back, really, to our first principles. Who do you operate on? Where did you put it? Can you get a better idea of what readout to use? That really may have impact on maybe the way we need to stimulate needs a little more nuance.
- Dr Mayberg: A first approach is to say, "Let's look at the who, because maybe we can just simply look at not everybody is getting the treatment that's best for them." That really requires us to understand, maybe people with high-negative mood, that are having trouble moving, really need to get the Area 25 target. Whereas patients that have more of a motivational problem and anhedonia might do better with the medial forebrain bundle, or the ventral capsule target. That's a testable hypothesis once we feel confident of how to optimize either of those two treatments. While this is a wishlist, I think we're far from that.
- Dr Mayberg: Another strategy that we've taken, and this is work from Ki Sueng Choi in our lab, and he's now funded as a Young Investigator by BBRF, is to look at what is the variability in brain scans in different kinds of TRD patients. Because over the years we've had many studies using functional MRI or PET scanning to actually map out patterns in patients that respond to different treatments, this was looking at data in patients who had failed treatments who started as never having been treated at all and then become treatment-resistant, patients who have been past responders who then fail drug and therapy, versus patients who actually have now failed ECT. With functional connectivity, with maps of the white matter, or with blood flow PET, we start to see abnormalities that are unique in these most severe

patients in this part of the brain, the midcingulate. That is an area that's part of our depression network. We're starting to get an idea that even within TRD, maybe you can look at symptom profiles, maybe you can develop an imaging biomarker for eligibility, but this is all work-in-progress.

Dr Mayberg: The one thing that we did focus on in Atlanta was actually a variable that we know we can control. That's actually where precisely we put the electrode. Because we looked exactly where we're putting it. We do scans to understand where we're putting it. The surgeon has a platform to do that in an incredibly precise way, so the obvious first question was to say, "Well, let's just look to see where the surgeon put it, and to look to see if there's a difference between people who get better, and people who don't."

Dr Mayberg: What we saw in Toronto, in a first analysis, is that while there's a lot of variation, responders are no different from non-responders. This really focused everybody's attention that maybe the big variable was patient selection. On the other hand, in Atlanta, we also saw that responders and non-responders had no variation at all, either.

Dr Mayberg: But we also had been thinking a lot about the fact that it wasn't just Area 25 we needed to focus our attention on. It was Area 25 and everything it was connected to. In Toronto, we didn't have the benefit of being able to do white matter maps, but we had the clue from the work in Toronto that the responders and the non-responders, while both of them showed PET scan changes in Area 25, surgeon did not miss changing activity in Area 25, but what was different between responders and non-responders was getting changes away from Area 25, remote in the network.

Dr Mayberg: Even here, in this little line drawing, if here's the target, we know we're hitting connections that are going throughout the brain, and it isn't random connections, but we can now map with white matter imaging techniques, diffusion MRI, and actually plot and look precisely, what are we hitting when we're in the target of interest? What are the connections that a given patient is impacting?

Dr Mayberg: What we did with a colleague, a biomedical engineer at Case Western, and again with Ki Sueng, and Patricia Riva-Posse, our lead psychiatrist, we modeled when you are stimulating on this contact on the electrode, what is the field of tissue that's activated around that electrode, and actually superimposed the model of the volume of tissue activated on the white matter maps. Those are the diffusion fMRI scans, and we generate what are called tractography maps, and that's telling us the white matter connections from the point of stimulation.

Dr Mayberg: What we did was to look to see, if you were well at six months, what map is being impacted? Which white matter is being impacted identically in anyone who got better? What we found was there was a very clear map that characterized everyone that got better. It was the exact same map. We could further see that if you were a non-responder

at six months, but you became a responder at two years, that we could actually appreciate that we had moved from a contact that had an incomplete impact on the white matter, to actually filling in certain white matter projections, both deep in the brain, and out into these areas into the frontal lobe.

Dr Mayberg: As you can see, there's tremendous overlap between non-responders and responders. It wasn't as though non-responders had no impact in the right place, and had no effect. They were partial responders, and became complete responders when we impacted the brain in total.

Dr Mayberg: What we're able to see is that this map reflected that fact that when we put the electrode in and around Area 25, we hit four distinct white matter bundles in the brain. We hit, in yellow, the cingulum bundle. We hit, in red, the connections between the two hemispheres, the forceps minor. We hit the connections down to the amygdala and hippocampus, that's called the uncinate fasciculus. We even could hit fibers that went deep into the brain, into the brain stem, the basal ganglia, and the thalamus. We now have, actually, a blueprint for what we need to target, and not just a blob at Area 25.

Dr Mayberg: Again, we haven't proved anything yet. We have a hypothesis. So we got a new group of patients, and we implanted this time by actually following this white matter blueprint. This shows an individual subject, their individual tractography map that we generated prior to surgery, bring to the surgical suite, and actually help the surgeon to implant the electrode so that it will intersect these bundles.

Dr Mayberg: When one stimulates within this network, and doesn't make any changes over six months, we did this in a group of 11 patients, instead of a 41% response rate at six months, we had a 73% response rate that increased to over 80% by the time we got out to one year. We made no changes in who we recruited, how we stimulated. All we did different was follow the white matter map.

Dr Mayberg: A very interesting also became observed by having done this white matter map. We actually saw that people got better at very different rates, as we went from just estimating the anatomy, to doing the tractography, to our latest group of patients, where we actually test, in the OR, with stimulating repeatedly. Instead of actually getting better slowly, as we see with most kinds of medication, that actually we start to get improvement much more rapidly. The more precise our targeting, and the more stimulation we give early, the faster they get better.

Dr Mayberg: We really want to try to understand the idea that maybe there's a clue to the mechanism of Deep Brain Stimulation by actually following the trajectory of the clinical changes. What we've started to know is the patients were telling us that this was happening, because in the OR, we would have them say things like, "What did you do?" There was a lot of behavioral changes that happened, when you were in the right spot, in the OR.

- Dr Mayberg: But that was very different from what they would say over weeks to months, where suddenly, it wasn't just that they shifted in terms of feeling sick and stuck. But they actually started to realize that they needed to do work themselves to get better. That wasn't something that they could appreciate before the operation.
- Dr Mayberg: We really need more readout to understand the difference between how to make measurements of what's happening at the first presentation of stimulation, and how to follow people over time. I just want to make the point that this idea of a very rapid change, followed by a very more protracted and chronic change, we see this now with other treatments. The availability of ketamine, which can actually effect a very rapid change, overnight in many cases, a very rapid anti-depressant effect, has some familiarity to us of what we see in the OR with these rapid switches.
- Dr Mayberg: The difference is is that ketamine actually will lose its effect over days to weeks, and the new indication does require repeated use of dosing of the ketamine. That I think that when we also think about the chronic effects, and the sustained effects with medication, we think about it takes time to grow new synapses, grow new neurons, and so it's attractive to think that there are certain mechanisms that can happen fast, and other mechanisms that happen slow.
- Dr Mayberg: We have evidence of this in our PET scan studies, where actually changes in Area 25, in the insula, and even in the thalamus, are actually present very fast, and with continued stimulation over a month, or six months, are actually not further changing. For areas that are remote from where we're stimulating, like prefrontal cortex, or the posterior cingulate, actually don't develop until late. We have evidence that the time course is reflected by changes in different brain regions at different rates.
- Dr Mayberg: You can ask yourself, "Well, why does that really matter?" Well, it matters because as you're tuning a patient, we tend to use the same settings for all phases. But we see that people have variable response rates, and so we really need better readouts of how the brain is changing over time.
- Dr Mayberg: We also need to understand, as you can see by these average depression rating scale scores, that even if you're actually in the response range fairly early, the scores start to bounce around. They really start to bounce around at about three to four months. The questions is what does this instability mean? Does it mean you need to turn it up, or are you actually starting to show normal reactions to life stress? At the care delivery side, we need to know when the device needs to be adjusted, or when your therapy might be more effective if one was more aggressive with it.
- Dr Mayberg: We've started to think about how can you track the chronology of these effects over time. What we've started to do is to start at the beginning. To go back to the operating room,

and really try to characterize what happens to a patient's psychic pain the moment you're stimulating in the right place, as defined by the tractography.

- Dr Mayberg: What we see is patients have two kinds of effects. That when you stimulate along the electrode, certain behaviors can change where you feel lighter. You can breathe. There's a change in the state of your body, even the lights seem to turn up. Then there's a much more profound kind of change, where you actually feel that you can move. There's a combination of less negative and more interaction outside yourself. This actually happens quite rapidly.
- Dr Mayberg: We can see that this Type One kind of change happens when you hit the cingulum bundle in our template, and this much more elaborate and important exteroceptive work, connection to the outside world change, is when you hit forceps minor. We're starting to see how different parts of stimulating the network even account for acute changes.
- Dr Mayberg: What Allison Waters did, which is one of the most remarkable findings we now have, is she can track what is the effect throughout the network by measuring electrical activity on the cortical surface. With EEG and stimulating off the electrode, she can see that there's 100 milliseconds where there's a very specific pattern that's repeated in the brain, every 100 milliseconds, that actually reflects stimulating in the right place. And that that pattern is stable in a person over months. It is the same pattern in everyone that's being stimulated in the template.
- Dr Mayberg: It can be used to see that you're in the imaging-determined right place, versus the adjacent contact that you might not pick based on the imaging, that if you actually have anatomical deviation, you can actually see differences on the cortical surface. This can be a verification that you're in the right place. You can do it in single subjects, and we've actually moved to actually see if we can verify we're in the right place with stimulation in the operating room.
- Dr Mayberg: The other thing we've started to do in the operating room is to actually realize that we can capture this switch between being profoundly ill at the start of the experiment, and actually feeling quite well at the end of the experiment, by measuring electrical activity off the place we're stimulating. This is a lot of fancy classification on algorithmic work done by Mo Sendi, a student in the lab.
- Dr Mayberg: But importantly, what you're able to see is that going from baseline to the end of surgery gives us a very specific, what's called an oscillatory change in the brain, where the beta activity is suppressed, and the right alpha activity is increased. The findings in this left-sided beta suppression is actually correlated with the carryover of the good behavioral effect for one week.
- Dr Mayberg: What you can see here is by giving 10-15 minutes of stimulation in the right place in the operating room, we actually get an almost complete anti-depressant effect in many

patients that stays off a week after surgery, two weeks after surgery, and then starts to go back to the baseline, but never back to the true baseline. Actually, we effect a change, a reset, that never goes back to its starting place, even by giving just stimulation in the operating room.

Dr Mayberg: We've actually now taken that finding, and because this battery now allows us to measure this electro activity all the time off the device when patients are home, we can start to look at how electrical activity in Area 25 changes over time as patients recover. We've started to see a pattern that the left side shows one pattern, the right side shows another pattern, and that we can look every week, or every day, at how this electrical signal is changing, and actually see that here in yellow, the electrical signal is stable if the patient is well.

Dr Mayberg: Here, you start to see that it's switched. It's stable here, and then it's starting to drop, and that actually predicted that this well patient started to relapse. We're starting to use these readouts, that we can do in the patient at home, that can give us an indicator that they may need an adjustment, or that they're about to get sick. This has really changed the game for us.

Dr Mayberg: The last thing I want to talk about is, all of this so far has been dependent on reading and using patient self-report and rating scales. In fact, you don't have to be a psychiatrist, and you don't need to be doing rating scales to see that this patient really has a distressed look, and the patient when she's well looks like a different person.

Dr Mayberg: It is so clear, that the first thing you notice is that patients just look different, and then they move, and then they do things, and then they feel better. If we're trying to use the rating scale to make decisions, the rating scale can bounce around. Making decisions on when you change the device really is confounded over time.

Dr Mayberg: We don't know, as you go longer and longer with stim, what's a stalled response, what's an impending relapse, and what's a transient life stressor. The question is, can we use something other than rating scales?

Dr Mayberg: Just to give you a flavor for where all the work is going, Sahar Harati, a computer science student, and Andrea Crowell, our psychiatrist, actually during Andrea's interviews, we would actually do videos, and what Sahar did was take the face video and actually do an algorithm analysis to see if she could actually tell the state of the face as a function of what Andrea said was the state of the patient.

Dr Mayberg: Andrea gave her three videos for each patient, where the patient was definitely ill at the beginning, definitely well after six months, and then this rough patch, where Dr. Riva-Poste, Dr. Crowell have to make a decision about changing the device. What Sahar was able to derive from these analyses of the face was that this rough patch wasn't its own state.

- Dr Mayberg: In some patients, when the psychiatrist thought it was a rough patch, sometimes the patient was actually needing to be turned up. They were sick. At other times, they were actually well, and needed to stay the course. That there was no intermediate state as far as the face was concerned.
- Dr Mayberg: That has real implications, that think about how you might make adjustments. That what a patient says, isn't the same as how a patient looks and acts. What we're doing now, and what Sahar did brilliantly, was to look at the quality of the voice, to look at this faceprint, and the self-report ratings, and to actually see which one of these best predicts the eventual response at six months.
- Dr Mayberg: What she found was that at eight weeks, a combination of the face and the voice was extremely good, at the level of 81% accuracy, to predict that a person was going to be better with continuous stimulation how they were being treated at six months, and that there was very little added value of doing the rating scale. We now, for the first time, have a way that the state of the body is giving us an indicator of the state of the depression without actually being confused by are they having a bad day? Is your depression getting worse? That the body is acting in concert with the brain, and that we have a new potential for how to track.
- Dr Mayberg: This is really a high area of focus for us at the Center for Advanced Circuit Therapeutics, and the new lab in New York. That the new team is looking to really exploit these other kinds of ways to measure how someone is doing beyond just self-report rating scales. Our new experiments, of which we're recruiting now, is a new prototype device that not only lets us record off the brain all the time, patient can help us to collect data at home in new and novel ways. With Brian Kopell, the surgeon here at Sinai, Martijn Figee, psychiatrist, Shannon O'Neill, a psychologist, we have a new team to really develop this technology.
- Dr Mayberg: I want to end with the idea that we've talked a little bit today about the roller coaster, if you will, of the last 15 years of DBS for depression. Again, this is called the Gartner Hype Scale, and in any new introduction of anything new, we go through the period of really inflated expectations. I think we had that early, that our early data was really encouraging. When the BROADEN study failed, and when the RECLAIM study in the ventral capsule failed, I think everyone got wildly disillusioned. But if you follow the data, the clues began to emerge. I think we're really now in this plateau of productivity, to really push this technology forward.
- Dr Mayberg: To end, I want to end with actually a metaphor from orthopedics, and not psychiatry. When your brain is broken, in some ways, it's like a really profound broken leg. You can try to just exercise, or use a cane. Sometimes you really just need to reset the bone, and you actually may need to pin it. That's actually not enough, because the bone needs to remodel and heal.

- Dr Mayberg: Then, after some time, once this is repaired, that's when the hard work starts. You've got to rehab. You've got to retrain. You have to relearn all kinds of things that were things you took totally for granted before you had the broken leg. It's only then that you can really expand your capacity.
- Dr Mayberg: What do we want with this technology? We need to have it get people better, and it needs to be not temporary. It needs to be sustained and durable. But we also need, now, new rehabilitative strategies so that we maximize recovery, and we really think about resilience for these patients. We have to teach people that distress does not equal depressed, and we need readouts to tell the difference.
- Dr Mayberg: My new sense of this is, for patients, how would you live your life if relapse was the exception and not the rule? I think that when you ask patients what they think about that, they get it, but it actually takes them time to fully appreciate it. As one of the patients sent, she sent this beautiful card, and I think it sums up how all of us think about life. It's really hard, but it's worth it.
- Dr Mayberg: As one of our patients said, and I'll end with this, you really have a lot to learn. That she feels quite lost, but it's nothing like it was before, when she was sick. She's just trying to figure out who she is, and where she's headed, and I think importantly, sometimes she's unhappy. She's often overwhelmed, but she's not sick. I think that's it, is how do we get people out of an episode, hold their brain in the right place, and let them be who they choose to be?
- Dr Mayberg: I'll end there. If you have any interest in more information, you'll find the information at our website, and you're free to write me, and I'll try to be as helpful as I can. Thank you.
- Dr Borenstein: Well, Helen, thank you for an outstanding presentation. Your passion, the amount that you care about helping people, comes across in every word. I've known you for years, and know that, but it so clearly came across in today's presentation. I think that you demonstrated really how from some very basic ideas of what area maybe should be stimulated, to then doing the work, following the patients, fine-tuning it, how a new type of treatment can be developed that can potentially help many people.
- Dr Borenstein: We don't have much time, but I want to ask you one question, which is, if you look out five, ten years from now, where do you think we'll be at that point in time?
- Dr Mayberg: Thank you for that question, Jeff, and I apologize for going over, for people who had questions.
- Dr Mayberg: I think five years from now, ten years from now, well five years is a little short, and we'll be doing our grant, so I hope I don't be obsolete before I get done. I'm hopeful that this kind

of research within these invasive devices will teach us about depression enough so that actually we can move and no longer need to implant.

Dr Mayberg: I think that this is the best chance I've had, in the 30 years I've been doing this work, to actually feel that I'm learning what depression really is, and what part is the reaction to depression. I'm hoping with these intense, invasive, carefully monitored studies, with these devices that allow us to record from the brain, we're going to actually learn what it is more, so that actually we can develop techniques that don't require surgery.

Dr Mayberg: I think it's going to fundamentally help us to know how to make our own selves obsolete in this business. I think that there are so many clues of how our rapid effects might be related to ketamine, that we can really start to put our heads together as a scientific community to see where we're seeing scientific points of overlap, and that's going to really help us to move to the next stage.

Dr Mayberg: I think that, in the short-term, this can be very powerful for patients that really don't have other options. But through this research, which it is now, it's research-only, it's going to lead us to ways of thinking about depression that we really can't even imagine at the present time.

Dr Borenstein: Well, thank you for that vision, and thank you for all the work that you have done and continue to do. I also want to thank our audience for joining us today. **The research that we fund is made possible through private donations, so please consider making a donation by visiting our website: bbrfoundation.org, or call us at 1-800-829-8289.**

Dr Borenstein: This webinar has been recorded. If you've missed any portion, or would like to share it with family or friends, please visit the Events and Webinars page on our website. I hope you'll join us again next month, when Michelle Pelcovitz, assistant professor of psychology at Weill Cornell Medicine NewYork Presbyterian will present [Integrating Virtual Reality into Psychotherapy for Anxious Youth](#). This webinar will take place on Tuesday, November 12th at 2:00 p.m. Eastern time.

Dr Borenstein: Once again, thank you for joining us. Have a good day. Take care.

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