Chris Rozell explains how brain stimulation and AI are helping to treat mental disorders

Rozell and his colleagues, using deep brain stimulation and explainable artificial intelligence, have developed tools to help people with treatment-resistant depression.

12 AUGUST 2025 | by PAUL MIDDLEBROOKS

This transcript has been lightly edited for clarity; it may contain errors due to the transcription process.

Chris Rozell
Increasingly, with the way brain-computer interfaces are making their way into popular culture and popular language, we can even start describing it as a type of brain-computer interface, but for people with psychiatric conditions. It's bigger than any one of us, it's bigger than any one thing that we can hold in our own expertise. Bringing together scientists of different stripes, engineers of different stripes, clinicians of different stripes, the lived experience voices, the magic for me happens where all that comes together.

Take a piece of brain data, put it through the encoder, get into the latent space. If we then move along that one special dimension, what changes about the brain data when we reconstruct it through the decoder is something that will change that classifier's mind about whether that brain was sick or well.

[music]

Paul Middlebrooks
This is “Brain Inspired,” powered by *The Transmitter*. Hi, everybody. I am Paul. We, as in humanity, are in an exciting time in the cross-fertilization of the neurotechnology industry and the cognitive sciences. My guest today is Chris Rozell, who sits in that space that connects neurotech and brain research. Chris runs the Structured Information for Precision Neuroengineering Lab at Georgia Tech University, and he was just named the inaugural director of Georgia Tech's Institute for Neuroscience, Neurotechnology, and Society.

This is the first time on “Brain Inspired” we've discussed stimulating brains to treat mental disorders, I think. Today we talk about Chris' work establishing a biomarker from brain recordings of patients with treatment-resistant depression, a specific form of depression that we discuss. These are patients who have deep brain stimulation electrodes implanted in an effort to treat their depression. Chris and his team used that stimulation in conjunction with brain recordings and machine learning tools to predict how effective the treatment will be under what circumstances and so on, to help psychiatrists better treat their patients. We'll get into all the details and surrounding issues of that study and that work.

Toward the end we also talk about Chris' unique background, and path, and approach, and why he thinks that interdisciplinary research is so important. He is one of the most genuinely well-intentioned people I've met, and I hope you're inspired by his research and his story. Check out the show notes, where I link to the paper that we discuss and other relevant information that we discuss.

Thank you to my Patreon supporters. If you value this podcast, go to patreon.com/braininspired. Good things await you if you support this podcast through Patreon. Thanks as always to *The Transmitter* for their continued support as well. Enjoy Chris.

[transition]

Chris, one of the many things, a handful at least, maybe not many, a handful of things that I'm jealous of you about is that, and we'll get to your new position in a minute, but when you're sitting around the dinner table with family and friends and your cousin asks you what you do, you probably have a much more straightforward answer than I do. I get frustrated because I flounder trying to describe what I do, but you can easily say, well, how's this? “I stimulate brains to treat people with depression, mental disorders." That's a very quick, poor overview, but it's something like that, right?

Chris Rozell
Yes, something like that, and I'll say that wasn't always the case for me. My career has evolved over time. It's been very gratifying to be able to work more recently on things that have a direct health implication, and it does make the description easier. We try to understand the circuits in the brain that go wrong when someone has an intractable psychiatric condition like a treatment-resistant depression, and then we're engineers, we want to understand how we can intervene in those circuits. In our case, we do it often with things like deep

brain stimulation, which is a pacemaker-type implant for the brain. It does lend itself to something that is very easy for the layperson to understand.

Increasingly, with the way brain-computer interfaces are making their way into popular culture and popular language, we can even start describing it as a type of brain-computer interface, but for people with psychiatric conditions rather than for people with a paralysis or something like that that you might be more accustomed to seeing. It does take people by surprise sometimes because they don't know that it's a thing, but it is a nice, succinct description, and it is, of course, very gratifying and a privilege to be able to do work that has impact that people can appreciate.

Paul Middlebrooks
Okay. Yes, I will strive to obtain a position more like yours. Maybe I need to switch gears, just so I can explain more easily to people what I do, right?

Chris Rozell
I started in theoretical neuroscience.

Paul Middlebrooks
Oh, that, yeah.

Chris Rozell
It was very difficult to explain to people what you were doing and also what the value was.

Paul Middlebrooks
Yes, I know. The value, well, it will pay off in 50 years, I promise. That's the promise of that kind of research, right?

Chris Rozell
Yes. It's difficult, because as a scientist, I believe so much in the value of it, but when you're talking to non-scientists and to laypeople, theoretical neuroscience is difficult to describe what the value might be, especially if it's not in the context of a health-related condition. In the past, you might have said something that tied it to, we have to understand these things theoretically so we can build better AI systems. I think with all the recent advances in AI and, of course, some of the realization in the public consciousness about what an AI future might mean, I'm not sure if that would be as widely appreciated as it might have been 20 years ago when AI felt more like a distant future than it does right now.

Paul Middlebrooks
Yes, I hadn't thought about that. We will discuss a little bit of AI because you used AI in one of your recent research efforts that we're going to talk about that also used deep brain stimulation to treat people with depression. This is a pretty major and special study, and I think it received a lot of deserved attention. Did this paper get a lot of attention?

Chris Rozell
It did, which, again, we're very grateful for the way it was able to drive some conversation both in scientific circles and in the public circles about the value of interdisciplinary research that went well beyond the individual study. It did, and I think the reason for that, and we can get into as much technical detail as you want, it was one of the first times that we've been able to record from deep in the brain while someone is undergoing, in this case, deep brain stimulation for treatment-resistant depression, we're able to see something, even though it's still very limited, about what's happening in the activity in those brain circuits, and we're able to measure something objective that's changing. In psychiatric disorders, where a lot of the assessment is done subjectively—

Paul Middlebrooks
What do you mean subjectively? A clinician asks questions, a patient answers those questions, and then they infer a depressive or non-depressive state from it?

Chris Rozell
That's exactly what I mean. It's through the judgment of the, in this case, psychiatrist observing the patient, asking them questions, surveys that either the clinician is filling out based on those observations or that the patient is filling out themselves. They're very nonspecific instruments in many cases.

If you have a condition like a cardiovascular condition, we can measure your blood pressure. We can measure your lipid counts. If you have diabetes, we can measure your blood sugar. We have data we can collect. If you have a movement disorder like Parkinson's disease, we can measure things like the tapping of your fingers and the speed of that, or how long it takes you to walk across the room. We can measure something.

Psychiatry is one of the few branches of medicine where we don't really have good ways to measure data directly. That's what I mean when I say objective, that we can provide really concrete information about either a diagnosis, or in our case, we were trying to measure a recovery response. These subjective instruments, and I don't want this to sound pejorative to our clinical colleagues, because I think the psychiatrists that we work with are some of the bravest people I know entering into these spaces and are able to do incredible things out of the judgment that they've developed over years and decades.

I think they would also be the first to tell you that it's very difficult, especially when the patients are having a difficult time self-reporting what's going on in the moment, just to be very specific, in our case, it's very difficult to distinguish what depression relapse might feel like, as distinct from, say, an emerging anxiety that can even be arising because the depression is remitting. You're feeling new things that you haven't felt for a long time, you're maybe contemplating a new life, and that's worrying, "Am I still going to feel lonely even though my depression has lifted?"

In those moments, because of the dysregulation of the body and these emotional systems, those things can feel very similar, and the patients will tell you this, they'll say, "It's very difficult, the doctor keeps asking me, 'Is this anxiety or is this depression?" They'll say, "In the moment, I can't tell." Sometimes with the benefit of hindsight, they're able to go back and say, "Oh, that was different. That felt different in situation A from situation B." Clinical decisions have to be made in the moment, they don't get to be made with the benefit of hindsight.

One of the things we've been trying to do with these experimental investigational therapies is to think, how are they going to be managed by the clinical teams? Because the therapy isn't going to be adopted if the clinical teams aren't confident in their ability to management. We're trying to provide some objective information to inform their clinical decision-making.

It's combined together with all of their rich experience and knowledge, just as another piece of concrete information to help them distinguish what they're observing, and then make decisions about, in this case, whether a stimulator needs adjusting, or perhaps there needs to be an adjunctive therapy, a medication change, psychotherapy, social support, something else going on.

These are clinical definitions. Right now, even the scope of something like depression, you're defined through these very broad categorical and subjective statements. There are almost certainly subcategories of things going on. I think it's becoming increasingly a place of hopefulness that we can resolve specific deficits and specific circuits that are leading to the specific things that are going on. We're not yet at the point that we can measure, say, behavior and different clinical things objectively enough and in enough resolution that we can start to define these subtypes and then look at the specific circuit deficits that might underlie them.

I think that's a hope that we all have for the future, that we can get to a place where we can do that. That's not where we're at right now, but I think one of the reasons this paper generated some interest was it was a first volley over the net saying, I think that there's hope here. I think we can measure something from the brain, and we can tie it to something that's clinically meaningful and difficult to assess in the moment right now, which in this case is the patient's recovery status from their core depression as they're receiving this type of stimulation therapy.

Paul Middlebrooks
Yes, and in this case also, the measurements are somewhat sparse. You're taking a low-- not low quality, but very few measurements for what is a complex mental phenomenon in depression, especially treatment-resistant depression. Let me back up, because you were talking about the ongoing role of the clinician, and one way one could read this paper is, "Oh no, psychiatrists are going to be replaced because there is this biomarker that can predict earlier than other clinical measures, and so we can just replace psychiatrists." You're careful in the paper also to say this is just another tool in their toolbox essentially.

Chris Rozell
Yes. I don't personally see psychiatrists going away any time soon. We have a huge need in society.

Paul Middlebrooks
Someone's got to prescribe the drugs.

Chris Rozell
Even in the context of this therapy, I think the work that we're doing and the clinical collaborators that we work with, and primarily, I'll mention here that Helen Mayberg is my clinical partner in this and really a pioneer in the idea that depression could be tied to a circuit deficit that could be modulated with things like DBS. She's a pioneer in every sense of the word, and did these surgeries for the first time over 20 years ago when DBS was first-- shortly after it was first approved for Parkinson's. I think their first surgeries were in 2003.

Paul Middlebrooks
For treatment-resistant depression?

Chris Rozell
Yes.

Paul Middlebrooks
Oh, see, I'm so naïve. I did not realize how prevalent this-- that DBS-- Well, I guess they're different. I associate DBS with Parkinson's because that's the famous story, but I didn't realize that the treatment of this kind of depression, that DBS has been used for that for so long.

Chris Rozell

Yes, investigational use. For approved indications, you have movement disorders, so Parkinson's, central tremor, dystonia. You do have some other indications, including epilepsy, and under a humanitarian exemption, it is actually approved for OCD, although it's not commonly done because many insurance carriers won't pay for it.

Paul Middlebrooks
What does a humanitarian exception mean? If it's just very severe OCD?

Chris Rozell
When you have, and I'm certainly not a regulatory expert, but there are approval pathways when there are really a paucity of things that can effectively treat a disorder, and I think it's especially when it's a relatively small number of cases, so OCD being less common than, say, something like a depression or a movement disorder or something like that. Again, I'm not a regulatory expert, so that's my understanding of it.

Depression was first tried, like I said, by Dr. Mayberg and her team in Toronto at the time. Andreas Lozano was part of that team, so over 20 years ago now. There are a number of sites that have studied it in different ways using some different targets, although the target that Dr. Mayberg's work has led to is probably the most common target. There are others that other groups have tried, and other strategies, including personalizing the target for individuals, including doing closed-loop stimulation adjustment.

Paul Middlebrooks
Can you describe that real quick, just what closed-loop is versus open-loop, just for the—

Chris Rozell
Closed-loop would be you're recording a signal, much like we talked about, in this case a local field potential signal, so an aggregated signal of the neural activity in the vicinity of the electrode. In a closed-loop system, there would be real-time adjustments to the stimulation based on what was being recorded. Essentially, when people use this word, they mean it in a way where there is no human intervention.

Think about something like cruise control or autopilot or the thermostat in your home that's measuring. You set up what you wanted to measure and how you wanted to respond, but the system is going to automatically adjust the input, whether that's the accelerator pedal or the furnace in your home or something--

Paul Middlebrooks
For the DBS?

Chris Rozell
Right. You adjust the stimulation level. I think most people would consider what we're doing open-loop in the sense that that signal is not being used to directly drive the stimulation changes. In some sense, I think you could still say it's closed-loop, but with a—

Paul Middlebrooks
Gotcha, yes.

Chris Rozell
-and on a slower timescale. We're making changes on timescales that look like weeks to months, because in our view of what's happening, it's a slow disease. It resolves slowly. That's the timescale that we're making adjustments. When I say we, I'm talking about the royal we in a sense of the whole clinical team, because there's a psychiatrist that is managing the patients and making those decisions. We're providing data to try and help support those decisions. That is the goal, I should say.

The paper that you're referring to showed that there was information in that data that we should be able to use to inform. That's exactly what we're working at right now, is how does one actually move to a full decision support system where you can inform in a way that is helpful to the clinic-- We've yet to show that you can actually be helpful to the clinicians by informing them to this data.

Paul Middlebrooks
I guess the main thing the paper showed then in that regard is just that you can predict recovery rates based on these LFP signals which are fed through some machine learning and adjustments of the deep brain stimulation parameters. You can actually better predict the recovery than other markers that are known. How would you phrase that?

Chris Rozell
In this case, what I would say we showed was we showed good accuracy in predicting week to week whether the patient was still sick or had entered stable recovery, which you can only define retrospectively. For us, stable recovery means that their clinical scores of the survey instruments that we were talking to have dropped a sufficient amount, and there's a gold standard definition for what that means. The stable part is, for us, effectively, they stay there. They don't rise back up again within the six months of our trial, excepting individual weeks, because individual weeks, these survey instruments can pop around.

The scores can be quite high one week, and you talk to the clinical team and say, "Why wasn't an adjustment made there? You were using your decision, your own insight. Scores got worse. You didn't make an adjustment. Why is that?" They'll go look in their notes and

say, "Well, that was a week where maybe there was a letter from the IRS that they were getting audited and owed money. They were really stressed, but we could tell in that case that it wasn't their depression returning. It was just a stressful event." Individual weeks can happen like that.

Paul Middlebrooks
Is that one reason why you would not maybe want closed loop?

Chris Rozell
Perhaps, and I'll say there are groups exploring closed loop, and I'm very interested to see what they come up with. Just in our hands and in our approach to this, that's how we've approached it, but I would say that's one potential concern, is are you adjusting it more than is necessary, and does that have any detrimental effect on recovery? I don't know. I'm very excited to see what those groups are able to show with their approaches. This is a complicated disorder, and we need different shots on goal. We're all taking different shots, and we'll see what ends up being useful or not.

Paul Middlebrooks
You're from Michigan. Is that right?

Chris Rozell
Michigan, yes.

Paul Middlebrooks
A lot of hockey there. A lot of hockey for the shots on goal.

Chris Rozell
Exactly. I'm giving away my Michigan roots by using a hockey analogy.

Paul Middlebrooks
Yes. One of the reasons why I asked you about that closed loop, whether you might not want to do that, is because one of the things that you and your team found is that there's this sort of initial change in the LFP signals shortly after the stimulation that is counterintuitive to what you would maybe want to see, and then it takes a little time to level out and be in register with the predictive recovery. Is that a correct way of framing that?

Chris Rozell
Yes. That's a good example. The recovery of the patients in this trial follows a sequence that takes time, takes weeks to months. One of the challenges is it's different for every person. Some are quite fast responders. Some are much slower, take many months. Of course, some don't respond to the therapy like any therapy. The heterogeneous trajectories, the individuality of how they're going to respond is one of the challenges.

We see it happen in sequences, both in the symptoms, but also in the electrophysiology. In this case, I think what you're referring to is the signal that we're looking for is a combination of different oscillations. You may have heard of theta, delta, alpha, beta, gamma band oscillations. That just means frequencies or oscillations at specific frequency ranges.

Paul Middlebrooks
How much of each of the frequencies is dominating the signals at each time.

Chris Rozell
Exactly. Think of it like a symphony with different instruments, all in different registers. Which ones are happening at a time, or in our case, which ones are changing over months? In this case, eventually over the six months of our trial, we saw that there were some specific frequency bands that had to increase in order to indicate that someone had entered stable recovery relative to where they were when they started.

That's all well and good, but one of the potential interesting parts of this is that we knew from previous data testing when stimulation was first applied in the operating room that one of these frequency bands, in this case beta band activity, went in the other direction when you first applied stimulation. It went down. In fact, it didn't go up. That was actually predictive of how that patient was going to be feeling in a couple of weeks. The more it went down, essentially, the better they were going to be feeling.

Paul Middlebrooks
Also, it would go up with their feeling better, right?

Chris Rozell
Eventually, in our study. In the previous interoperative studies, we just knew that decreasing that frequency was going to be good a couple of weeks later. If you wouldn't have measured over six months, if you would have just taken that first bout to stimulation—

Paul Middlebrooks
You'd think, "Let's depress beta and that'll cure them."

Chris Rozell
You would have—

Paul Middlebrooks
Keep it depressed.
Chris Rozell
-go in the wrong direction.

Paul Middlebrooks
Yes. Keep it lowered. I shouldn't say depressed.

Chris Rozell
Yes, inhibit.

Paul Middlebrooks
Inhibit.

Chris Rozell
It was really, the advances in our ability to record from the brain, in this case by our commercial partner Medtronic, because they were interested in closed-loop stimulation for Parkinson's disease, they designed a device that lets you record chronically over time the local field potentials. Now that we have that ability, and we were able to approach something like the Brain Initiative from NIH and say, "There's been this technological advance. We can finally do this stimulation. We can record. We can see what's happening over time, and we can try and make the sort of advances that are needed to take this investigational therapy and really make it scalable and accessible to the broader population that needs it."

By measuring longitudinally, we could see that actually what we needed was an increase in this beta band activity for someone to be in stable recovery. Now, when we went back and looked in the chronic recordings in these patients, there was also this inhibition of beta band activity in the first month when we turned it on, that eventually, over a few weeks returns to baseline and then starts to facilitate as patients enter stable recovery.

I think the lesson here is that it was really important for us to collect this data longitudinally over six months and see, and that technical innovation was really critical, because otherwise we would have been, in some sense, chasing our tail a little bit by taking the short-acting effect of the stimulation. From a clinical point of view, that was a very important observation, but I think it's also scientifically really interesting. It tells you that, something that we might have suspected, given how long the therapy takes to work for a depression patient, that it's not just the impact of the stimulation directly that's affecting things, like you often see in Parkinson's. You change the stimulation, the symptom changes right away.

Paul Middlebrooks
You turn on the stimulation, the tremors stop.

Chris Rozell
Yes, within minutes, effectively they can tell something about how that stimulation change has helped or not. That's not the case for depression. One of the reasons we need these biomarkers, to help them know if the settings are right, but it also tells you, or is at least a very strong clue, that part of the recovery is some type of adaptation in the circuit. There's some type of plasticity going on. It's not just the direct effect of the stimulation. It's non-linear. There's something happening in the opposite direction from when you first turn the stimulation on.

It's a powerful clue that there's something adapting in the circuit that's part of the recovery, and that's one of our challenges, to figure out exactly what that means and whether that can be helpful in deep brain stimulation, whether that can give us clues to other methods of treating depression.

Paul Middlebrooks
One thing that springs to mind is there's a similarity, at least, with modern use of psychotropics. One of the interpretations of this longer term initial thing that then longer term goes into a different regime is that you're resetting the system. If you think of your brain activity as a surface with a bunch of wells in it, then this is a complete analogy, but, depression, let's say, you can get stuck in a well, and then by stimulating, you can think of it as flattening out the wells and letting the brain settle back into a healthier state where you're in a better well, for lack of better analogy. Things like, well, psychotropic drugs are thought to work somewhat in the same way. I don't know. How do you think about that?

Chris Rozell
Yes, and I have to say that I am certainly not an expert in psychotropic drugs, so I'm not going to speak too directly to that, but I do think that matches our conception of what's happening with deep brain stimulation, that there is an acute effect, a short-term effect, a fast-acting effect that is a type of kicking the system out of a bad state. We can see that happen sometimes with just a few minutes of stimulation in the operating room.

Paul Middlebrooks
This is in a very circumscribed brain area. You think of like if you take acid or something, it's like, oh, your whole brain is going berserk, but this is a very small brain area that you're--

Chris Rozell
It is, but this is a network disorder, and the targeting that Helen Mayberg and Ki Sueng Choi and Patricio Riva-Posse and others have very carefully done through imaging over the years is really focused on hitting a highway junction. It's targeted through looking for an intersection of white matter bundles, four of them specifically, that reach through different major systems in the brain that we know are implicated in depression.

Yes, we're targeting one specific area, but that area is not a gray matter target like you might think of in Parkinson's, it's a white matter target that reaches into multiple major networks in the brain. It's really a super highway hub for many of the functional networks that you hear about, default mode networks, salience network, the attention networks. It's a hub where many of these networks have some intersection point.

Paul Middlebrooks
Then you've got to be cautious because there's lots of stuff that could go wrong as well, right? You could be resetting other mental phenomena in negative ways, perhaps.

Chris Rozell
Yes. We don't see direct negative side effects of the stimulation, which is obviously a concern that's monitored for. You're affecting a network. Certainly, there are going to be many changes, we hope most of them the right changes that move people toward a recovery.

Paul Middlebrooks
I wonder what the-- You might know the answer to this already because I'm not sure how you followed up or planning to follow up. I can see a scenario where there's less default mode. Default mode network is often associated with an internal monologue, your internal states and thinking and daydreaming and stuff, and I wonder, because depre-- I'm not an expert on these things anyway, so I'm talking out of hand here, but you can perseverate in those states when you're in a depressive state, and I wonder if it's associated with less default mode network, essentially.

Chris Rozell
Yes, I'm certainly not an imaging expert either, but it would also be my understanding that you see, in some sense, an over representation of things like default mode network, which is often characterized by internally-driven thought. In a clinical context, you might call it rumination.

Paul Middlebrooks
Rumination, yes.

Chris Rozell
Both an over activation, and maybe some degree of over connectivity. Again, I'm not an imaging expert, but I believe that that's been studied quite a lot with different types of therapies, both pharmacologic and TMS and DBS and things like that.

Paul Middlebrooks
What you saw in your study is that the health of the white matter is also predictive. Since you're talking about the superhighway of the connective cables, essentially, between neurons, so the health of the white matter was actually very predictive of the depressive results, right?

Chris Rozell
That's right. Just back to your previous statement about short and long-term effects, we do see short-term effects, but then also these longer-term symptom resolution, and we have this notion that there's something adaptive happening. We don't know yet what it is, but of course an intriguing clue is what you're mentioning, which is the imaging team on that study was able to look at those patients, and certainly, there's been a lot of work trying to concord imaging findings with symptoms.

This is a very small study, but now that we had an objective marker and not a more subjective symptom, your base description, the imaging team was able to look at the objective brain recovery and say, "Okay, this person responded very quickly. This person responded over many, many months. What's different in the brain imaging at baseline?" Because in these patients, we weren't able to put them back in the scanner once they were implanted. We can do that now because the current commercial devices are MR-compatible, at least to some degree. At the time, we couldn't. This was all before they had surgery.

I think one of the incredible things that the imaging team was able to find is that there was a correlation with, I'll say, structural abnormalities in the brain. It's imaging, so these are, in some sense, indirect measures, but it was most consistent with something that looks like demyelination. Some focal areas of myelin abnormality in specific places, and then using something like a functional connectivity, which is more of an fMRI-based technique, where you're looking at correlations between different brain areas. Looking at our stimulation sites and other sites, there is a deficit in functional connectivity that spanned across that abnormality in the white matter structure.

We don't know how that got there. Of course, we don't have that type of imaging data long-term on patients or any other notion of what's going on, but it was a very compelling finding. To me, one of the most exciting findings in the paper was this concordance. It did also correlate with essentially the number of depressive episodes, so how long a patient had been sick before they enrolled in the trial.

We don't know, certainly, the causal connection there, or whether there is a causal connection, but there's something to look at there about whether a degree of illness, either characterized by the history or how long it takes someone to get better, whether that is causally connected to these structural and functional deficits in the white matter of the patient. That is very intriguing, but there's a lot we don't know yet.

Paul Middlebrooks
Yes, so demyelination is associated crudely, I guess, with slowing of the propagating nerve signal, and diseases like multiple sclerosis is a demyelinating disease, essentially, where all sorts of things go wrong.
Yes, that's interesting. A slower cable transmission is a very crude way of saying probably what's happening, because all sorts of things could be happening, and as you're saying, you don't really know.

Chris Rozell
Yes, from an electrical perspective, you would expect slowing and some signal loss of myelin--

Paul Middlebrooks
Yes, right. Unequal transmission of signal--

Chris Rozell
Yes, exactly. That's a very crude first approximation in electrical terms. You will say is multiple sclerosis is a much more global net for the brain. Here we're talking about what seems to be very focal abnormalities.

Paul Middlebrooks
Right at the hub, right at the superhighway hub.

Chris Rozell
Not at the stimulation site, but within the network that we're treating. A few different places in that network, but there was one specifically right at dorsal anterior cingulate to mid-cingulate boundary, so one of the major white matter branches. There are a few others in the different circuits, but that's one that's been most reliable in our analysis.

Certainly intriguing to us that we might be able to someday understand the subset of depression patients that are helped with this therapy and be able to describe it as a singulopathy, a deficit in a specific circuit that there may be all different types of therapies that we could bring to it to try and correct that deficit.

Of course, that is a vision for the future, but I think that's the sort of hope that gets sparked in me with the really excellent work that the imaging team was able to do there to identify these abnormalities that correlated with the activity in the brain that we were able to see, and then even some of the behavior that we were able to measure in the patients. We were recording their face during their clinical interviews and their voice, and we were able to see changes in their-

Paul Middlebrooks
It's crazy.

Chris Rozell
-behavior, that change, at the same time, roughly speaking, that their brain entered stable recovery.

Paul Middlebrooks
I was going to zoom out in a little bit because there's a little bit more from the paper that I want to discuss, but let's zoom out now and talk about the current state of neuromodulation, brain stimulation, with respect to just the history of where we've come from. This was like electroshock therapy back in the-- I don't know, was late 1800s? I don't know when all this stuff started happening.

Of course, there were ice pick lobotomies back then, which is not neuromodulation, that is complete ablation, removing parts of the brain or connections in the brain to treat people. Those seem very crude. We look at those as if like, "Oh, how could you have done that at the time?" Then fast forward to today and things are much finer-grained. You were just talking about how you can target areas much more specifically instead of just bathing the whole brain in some pharmacological agent without specificity to a target area.

I still think of DBS, deep brain stimulation, like in the Parkinsonian way, you're still going in and zapping. Here, let me give an example. When I was a eye movement neurophysiologist, eye movement and cognition in non-human primates, one of the ways, well, the way that we would ensure that we were in the right brain area, which in my case was frontal eye field, was one of the brain areas that we studied, you would stimulate past some tiny currents, well, tiny to us, but really large to the brain. You would zap the brain. If they move their eyes reliably, when you zapped, you knew you're in the frontal eye field.

I always thought like, "What is that subjectively? What am I actually doing to the brain there?" It seemed crude, even though it was very specific. Where are we, do you think, in terms of the sophistication, let's say, of these kind of stimulation techniques?

Chris Rozell
Yes, I think it's a great question. Certainly, I think you're bringing up an important point, which is the history of developing new interventions for psychiatric disorders is a complicated one, and especially around psychosurgery is a complicated one. You're bringing up, you called it electroshock therapy, but electroconvulsive therapy is used today and is a very effective therapy for a lot of patients. It's a life-saving therapy.

Paul Middlebrooks
It's milder now, right?

Chris Rozell
There certainly have been changes, is my understanding. Also, a better understanding of side effects and how and when to deploy it. Again, that's not my area.

Paul Middlebrooks
For how long and for how much current and et cetera.

Chris Rozell
I don't want to speak to it too much in detail because it's not my area. I will say the broader comment that I'll make to this is, I think as we've seen the advances over the last decade, I've been very heartened to see that there is an emphasis being placed on ethics as a part of the conversation whenever science and technology is being developed, at least in the context of the things that we're doing, so I'll speak just to the Brain Initiative, which is where a lot of our work has been funded from. I was very heartened to see that ethics was a part of the discussion in the Brain Initiative very early on.

Paul Middlebrooks
What aspects of ethics are you talking about?

Chris Rozell
Even just bringing into the conversation that ethics has to be a part of the conversation. For instance, you have questions for us, might be relevant to how and when our patients consented? How are you getting informed consent from someone who is in a psychiatric disorder and so on? It's not even a specific issue, it's just the fact that's an important part of the conversation. The other thing I'll say that's been a passion of mine to try and bring out and I see it emerging more and more in the community is the lived experience voice.

Paul Middlebrooks
Oh, yes. We'll reflect on this workshop that I went to at your institution, but go ahead.

Chris Rozell
Yes. I'll say, one, the studies that we're doing right now, one of the most important things driving what we're doing is actually capturing the stories of the patients, what is frustrating for them, the clinicians, what is frustrating for them, and then turning that into research questions.

Paul Middlebrooks
Taking anecdotes and using those anecdotes, not as evidence, which is poor science, but to ask the right questions.

Chris Rozell
Exactly. We can see that the patients are frustrated at having to try and describe in the moment whether what they're experiencing is depression or anxiety. They're saying that to us very explicitly. The clinicians are reporting the challenges in resolving that. These are lived experience stories of the people in the room at the moment. As you say, that's not data. Those are anecdotes, but you hear enough of those anecdotes and it starts to bubble up. This is an important question for us to try and address.

I'll say that's something, again, to bring up my partner and collaborator here, Helen Mayberg, that I've always admired about her is the willingness that she has just to listen to what the patients are saying and then try to understand how to pull that together and describe it and form questions out of it. Despite our need to make objective measures, one of the things that drew me to entering into this partnership was the emphasis on starting from just listening to the experiences of the patients.

I'll say on another project that we're starting up, where we're trying to do new behavioral experiments and measure brain body interactions and trying to understand these things that I was mentioning earlier, we have lived experience people with intracranial implants as part of the research team. The chair of the council that we're starting there likes to say, "Nothing about us without us." I think that we're hearing more and more a willingness from companies and from researchers to bring the lived experience voice into these discussions. I think there's a lot more we can do with that that I'm very encouraged that we're starting to hear those voices, the voices of our ethics colleagues and the voices of our lived experience partners be part of these conversations. Yes, it is a complicated history. Those are the things that have me encouraged about what we're doing right now and looking to the future.

Paul Middlebrooks

There's a lot of talk among some groups, some circles about needing to bring in the subjective experience of organisms of humans in any question. In some sense, it's so daunting because there's such individual variability, variation, and we confabulate all the time, so we have to use words to communicate and words fail us. Yes, they never seem to fully explain what I'm trying to explain, et cetera. It's like, you've done this great thing, and you can predict these long-term using this biomarker, you can predict recovery. Ain't that enough? You got to take everybody's subjective experience into account. This is the goal, right? It's like the reason for doing this.

Chris Rozell
Yes. No, exactly. I think you're right that we're aiming toward objective measures that we can make concrete decisions about treatment on. Of course, someone feeling better is the ultimate goal. We also have to acknowledge, especially along the path to recovery, that sometimes the feelings that they're able to describe are not one-to-one correlates to what's happening in the biological system that needs to be managed as part of the recovery.

The subjective stories are what get us to the questions that we have to ask. Of course the experiences in total are the important metric. If we were developing a therapy that helps some objective biomarker, but at the end of it, everyone was saying, "I still can't work. I still can't enjoy my family and my relationships. I still can't live a life that feels fruitful and I feel happy with," that's not a success.

There's this balance of knowing that sometimes the subjective descriptions are not operationally helpful at every intermediate waypoint, but still valuing the stories and the experiences on the whole, both to drive the questions that are the important things we're trying to pursue. Also, eventually as our outcomes. You're right, that language is often insufficient.

Paul Middlebrooks
Mine is. [laughs]

Chris Rozell
Yes, no, all of ours is. For me, there are two avenues that we take when our language is insufficient. One is data and trying to make things objective. That's the path that we're on here scientifically. The other is art. It's one of the great-- redeeming things about art is it's able to express something about the human condition that goes beyond the words that we have. Now, that's not operationally useful in a clinical sense, but it's very important to our humanity. For me, there are these two branches when our language fails that we can use to try and describe things. One of those has some clinical value. One, I think, is deeply rooted in our humanity.

Paul Middlebrooks
We've known for some time, we, not me, have known for-- we as humanity, as the clinicians, have known for a long time how long depression takes to treat, that it's a slow wave sort of thing, right? You've corroborated this in terms of the biomarker and predicting it's still slow wave. Has this work taught us anything new about the nature of depression itself?

Chris Rozell
I'm not sure yet. First of all, I want to clarify, we're working with treatment-resistant depression. There's a very specific--

Paul Middlebrooks
How does it differ? Can you just speak to what's the-- there's not a bright line, is there? I guess there is, if you have to give it name.

Chris Rozell
There are different definitions that people use, but broadly, I would say many treatments have to be tried and are no longer effective, and we could-

Paul Middlebrooks
No longer effective. They could have worked for a while and then its efficacy is lost.

Chris Rozell
Not uncommon for some treatment to work for someone for a period of time, but to start to lose its effectiveness.

Paul Middlebrooks
Yes.

Chris Rozell
Of course, some treatments never work for some individuals. While you can use different definitions, I would say they all have, as a function, that the currently approved treatments, how many medications do you have to have tried? Many of the patients have tried a dozen, two dozen medications, but you have to have tried things that are not currently working for you, and that has to be persistent over time.

I think in the paper, you're referencing, the average time in the current depressive episode was on the order of four years. It's persistent over time. That's a feature of the diagnosis. If you look at the DSM criteria, the manual that's used to define what a diagnosis for a psychiatric disorder is, for depression, there are two core features, one related to mood, one related to interest in activities.

Paul Middlebrooks
Physical activities or just activities in general?

Chris Rozell
Activities, working activities. What we might call anhedonia, like lack of joy, lack of pleasure. There are a number of secondary symptoms. You have to have some number of those. Those would be psychomotor symptoms. People often are slower in their movement, in their speech, things like this. You have to have at least one of the core symptoms, some number of the secondary symptoms, but the point I'm trying to get at is a key part of the definition is persistent over at least two weeks most of the time. It's a feature of the diagnostic criteria that it's a persistent condition over time.

Paul Middlebrooks
Okay. We're not talking bipolar, et cetera?

Chris Rozell
We have a completely different diagnosis. I'm talking about unipolar major depressive disorder here. By the time they're getting into a study like ours, they're treatment resistant, they've been sick for a very long time, they're not responding to anything else. Whatever is happening in the brain at that point might be and almost certainly is very different from the person who's first presenting to their doctor saying, "I'm not feeling quite right lately." First maybe coming on to an SSRI or some psychotherapy, some other first-line treatment. Almost certainly there's something different at that point. I think it's yet to be understood. Now, as we see these structural things in the brain, these abnormalities that we've pointed out, I think it's an intriguing clue, but we don't yet know whether that wind its way all the way back to something that would be identifiable in a first-line depression diagnosis. I would be very suspicious of that.

I think we're talking about a very specific class of patients. Patients that are enrolled in our trial, so being selected through a subset of psychiatrists, maybe not even all treatment-resistant depression, maybe just collections of symptoms that are being identified as being particularly approachable with this specific therapy. I don't want to over-read into what's been found. I'm hopeful it can help us understand something, but there's a long way to go to connect those dots.

Paul Middlebrooks
Yes, all right. We all know the brain is a complex system. I had Nicole Rust on a few episodes ago, and one of the things, or a major emphasis in her book is that, historically, we have not treated the brain in our research and/or treatments as a complex system, and that we need to start treating it like a complex system if we want to understand it and treat it better.

I've always heard and thought of complex systems as being robust. She agrees with that, but she also makes the point that they're also fragile at the transitions, at these, well, maybe control knobs. There are these certain control knobs that if turned the wrong way, then all of a sudden it becomes fragile, like epilepsy or things like that with runaway activity, et cetera. Do you think that this is one of those sorts of control knobs that you can predict and understand and control a complex system via this--

Chris Rozell
Maybe some parts of it. Nicole and I have spoken about this, and I am so grateful for the work that she has done over the last few years to be introspective about our scientific enterprise and about our foundational research and how we can think about pointing our fundamental research toward things that more effectively result in cures and therapies.

I do resonate a lot with the dynamical systems view that she's taking on it, and certainly a lot of the way that we think about what's happening, specifically about a complex system, as Nicole and I have talked back and forth about this. I think it's a good question. Is a complex system controllable, or is that even what you need in this case? Because we're looking at specific activity in a specific circuit, maybe not even all the activity, just some aberrant part of that activity.

It's not usually how I frame things in my mind that there's some complex system that we're trying to control. It's more like the analogy that you started to use earlier, which is this complex system is moving. It's a dynamical system, and some part of it has been stuck in some attractor basin. With the onset of stimulation, it seems that we're kicking it out of that attractor basin.
Perhaps that's something similar that's happening with short-acting medications like a ketamine or something else short-acting like a TMS, but then also that landscape may need to change, which, just to get to the nuts and bolts of it, means changing something about the wiring, changing something about the circuit. When you talk about changing an attractor, you're talking about changing the topology of the network that is--

Paul Middlebrooks
That allows it to have the dynamics in a different way.

Chris Rozell
You're changing the wiring somehow. We don't know exactly what that means yet, but that's more my conceptualization, that you're kicking it out of a bad place, but then you want it to sustain this more typical and more healthy activity, and so the adaptation of that landscape is going to try and prevent the activity from sinking down into a negative mood state attractor like that.
I appreciate the framing in a complex system. It doesn't tend to be how I naturally think about it. I tend to think more in terms of attractors and dynamics. I think the questions are a good one, and it's not clear to me that we need to control the entire complex system. I'm not even sure that's what I would think about aiming for.

Paul Middlebrooks

Yes. Okay. The way that you're describing this is you kick it out of the bad state, but then you can't guarantee that it's going to land in a good state. You have to allow it to settle and then see where it lands. There must be some protocols that increase the likelihood that it'll land in a good state, or maybe that's a future endeavor.

Chris Rozell
It's a good question. Yes. I don't think we know something about that, but perhaps that's the fact that these patients are going to psychotherapy while they're recovering. I don't know. I'm just offering that as an example of conditions that could be constructed that might help that. I don't know. I think that's a really good question.

Paul Middlebrooks
Because it got in that bad state somehow in the first place, and it's probably likely to just go back to that same state if nothing else changes, right? Let's say you're changing the weights of all the synaptic connections, but then it just seems like if they have been in one configuration for so long, why would they then all of a sudden get better and change, right? It seems like you'd need something else to--

Chris Rozell
We don't know. We talked a little bit ago about these white matter abnormalities that we're seeing. Perhaps a role of that abnormality is it's allowing these basins of attraction that can pull to a negative mood state. Perhaps changes to that are something that could prevent it from being able to sink down to that type of mood state. We really don't know the mechanisms. There's going to be a lot of work that has to be done.

Paul Middlebrooks
You'd have to be injecting some neuropeptides to fix the white matter or something like that. Yes.

Chris Rozell
We don't know, maybe-- You're putting a stimulator in the brain. There are probably many more mechanisms going on than what we've been able to measure and what we've been able to understand so far. A lot yet to understand. It's not in my purview that I want all that activity to be controlled. We still have creativity. We still have thoughts. We're still living our lives. For me, my conceptualization is try and get a boundary up to keep it out of some bad places. People still feel sadness for very reasonable reasons.

Paul Middlebrooks
Oh, yes. That is a form of control. I don't think that Nicole means we need to control every millisecond of every aspect of the complex system. To be able to move, you turn the knob and you can move it in a definitive way. That is one version of control.

Chris Rozell
I guess maybe your definition there is, is it predictable what's going to happen when you apply your intervention. Right?

Paul Middlebrooks
Yes. That's a good way to put it.

Chris Rozell
We're seeing, at least in the subset of patients that are responding to this, that we see some predictability of what's going to happen. Maybe not always the timescale of the predictability and things like that, but we see some predictability. That's the biomarker.

Paul Middlebrooks
It's the humble version of control.

Chris Rozell
The crudest possible version.

Paul Middlebrooks
Can we just talk? I want to get on and talk about your new position and some of your back story and career, because you told me a story over breakfast and I want you to fill in some holes, and I want you to share that with the audience. Can I just ask you quickly about how you used AI in this endeavor, in the study? You're recording these local field potentials, and then you send those signals through what's called a generative causal explainer framework, which is like a machine learning model, essentially. Maybe just high-level describe that. Then what I also just want to know is, could you have done this without AI, without modern machine learning tools?

Chris Rozell
That's a great question. We were recording from one specific area in a network that we believe is being engaged by the stimulation. The question we started out with is, can you see anything changing in that signal that's indicative of recovery? I'll first say, before we get into any talk of AI, that the most important thing we did was define what that meant. It was not an AI question. It was a question about the experience of the clinical teams that have been working on this. Let me just give you an example of something that was not what we did. You have these survey scores that are being captured, say, every week when the patient comes in for their clinical--

Paul Middlebrooks
I'm feeling happy, I'm feeling motive, I'm feeling motivated, I'm feeling whatever.

Chris Rozell
That's a score. There's several instruments. The one we reported most often is called that Hamilton Depression Rating Scale, 17-question scale. There's a number that comes out of that. You might say, can you predict that number week to week from a brain signal? First of all, that did not work well when we tried it.

Paul Middlebrooks
Doing what? What method did you use to--?

Chris Rozell
We tried several different technical techniques, but generalized regression, let's just say. Then you reflect on it for a minute and you say, first of all, that's probably not even the right thing for us to be doing for the needs that we had articulated. We've already said, listen, one of our challenges is that the movement of this survey score from week to week is influenced by all sorts of things that are not necessarily just the depressive state. This has been documented that there are biases, there are recency biases. It's a nonspecific measure, capturing a lot of things like insomnia and--

Paul Middlebrooks
Oh yes. Which can be causal. It can be a cause of, and causal. It can be circularly causal.

Chris Rozell
Certainly known comorbidities, right?

Paul Middlebrooks
Yes, comorbidity.

Chris Rozell
Also, we can already collect this survey score. If that's all we need, we don't have to do any more work here. If that were sufficient for our needs, just replicating that is actually not a useful exercise. It's maybe a neat technical trick, but it doesn't actually get us anywhere.

Paul Middlebrooks
Because it already exists.

Chris Rozell
They already have it. We actually spent a lot of time in the early days of the project saying, you're telling us that there are things about this measure that you don't trust to the clinical teams. This measure moves, it's at the midpoint of the scale. It moves a little bit one direction or another. We see you not paying attention to that level of movement as you're making decisions about what to do. Maybe not paying attention is too strong, but you're not basing all of your decisions just based on that.

We started with the question of, what do you actually trust in this measure? You're obviously not trusting it where a movement from a 15 to a 16 is going to influence your decision-making. After a lot of talking and mostly listening, what we came to understand is there's a lot of trust in the extremes of the measure. A very high score, everyone can agree that that person is sick and suffering.

Paul Middlebrooks
15 to 17 or whatever.

Chris Rozell
Higher usually, but at the high end of this range, definitely sick. The clinical teams all agree about that. Once you get to the low end of that range, which on this particular scale, it's below an 8, but it's not specific to this scale, you get to that end of the range, everyone can agree that that person is--

Paul Middlebrooks
It's this valley of death in the middle that's--

Chris Rozell
In the middle, especially as people are recovering, and we spoke earlier that this recovery time can be very confusing, as they're feeling new things, the reports can be a little, not unreliable, but nonspecific.

Paul Middlebrooks
They confuse anxiety with depression, as one of the things--

Chris Rozell
They'll say, I can't tell the difference. What we came away with was what we can trust are the extreme points. We can all agree during time points when this group of patients, and in this case, it was the first month, this cohort of patients, a subset of them was very clear that everyone could agree that they were sick in that first month. Then in the last month, in this case, the clinical team, their combined years of experience in this, it was just a really remarkable clinical result that of that cohort of 10 patients, 90% of them were responders, which meant their scores dropped by half. That's what's the gold standard in a drug trial or anything like that. 70% of them were below the threshold for remission.

Paul Middlebrooks
It's amazing, by the way. It's just amazing.

Chris Rozell
It's a breathtaking slew of results.

Paul Middlebrooks
It really is. I just want to pause there and just soak that in for a second, for people to soak that in.

Chris Rozell
That's decades now. That was, maybe at the time, a decade, when we started that cohort, of experience with this therapy. A very experienced, very dedicated, very passionate, very smart clinical team, managing this. Of course, a little bit of good fortune is on your side too. That may not be the sort of number that you would expect to come out of a clinical trial or something like that.

Paul Middlebrooks
It's not.

Chris Rozell
It's a very fortunate situation as someone looking at the data, because we could get away from questions about response versus non-response, and we could look at a bunch of responders and what the idiosyncratic differences were in their response. In that cohort, there's a lot of agreement, in the last month, they're basically all well, except for the one non-responder who we can come back to.

We said that's what we can trust. Let's ignore all the data in the middle when things are very confusing and just start there. Then we're in very classic classification problems. We have labels that we trust. We did, in this case, a machine learning classifier. We tried several different kinds. It was all about the same. In this case it was AI, in the sense that it was multilayer perceptron, essentially. Not a huge one. These were not large data sets.

Paul Middlebrooks
This is great. Among the AI models, this is the most vanilla, basic model.

Chris Rozell
Exactly. Things that we've been doing for decades before we would even have called it AI most of the time, we would have called it just machine learning.

Paul Middlebrooks
It's feed-forward network.

Chris Rozell
Exactly. Feed-forward network. We tried several different kinds, including some things that, I don't know, today maybe you call AI, but we would have just called--

Paul Middlebrooks
Isn't that funny?

Chris Rozell
Logistic regression. There's a lot of robustness across these. Where I think we started to use the AI label a little more strongly was that told us that there was something changing between the two time periods, when they were sick and when they were well. Something in common across the group of people. It wasn't a model trained on each individual. It was one model trained for the whole group of responders. Then there's a natural question of what is changing. It's the classic complaint about machine learning or AI methods, that they're black boxes.

Both for clinical trust, but also scientific understanding, there's a real pressing question here of what is changing? How do we try to understand that? The technique that you're referring to, generative causal explainer, is a technique that we had developed previously in our lab for a type of what they call explainable AI. It's how you take these black box models and say something about what they're keying off of. What we did here, because a lot of the existing work was really assuming you were working with images, and what's the region of the image that is causing you to think that this is a bicycle versus a puppy dog, or whatever?

Chris Rozell
Not everything, but a lot of it was at the time that we did this work. We were just starting to get the early days of generative models working. This was before the big revolution in generative AI, but we were just trying to get things like autoencoders and variational autoencoders. We're just starting to get these AI models that could generate data. This is the basic technique. We train the black box classifier to distinguish sick from well, and then we fix that. Now that's a black box that we have.

We can put a piece of brain data into it and it can spit out a label and say, I think that brain is sick, I think that brain is well at that point in time when that data is collected. Now with that fixed, what the generative causal explainer is is essentially a generative AI model. In

today's terms, you might think about Midjourney or ChatGPT, but it's trained, instead of producing words and images, it's going to produce brain data. It's just going to spit out brain data that statistically looks like the brain data that we had recorded.

Paul Middlebrooks
It's like an autoencoder.

Chris Rozell
Yes. Variational autoencoder is exactly what it is. Here's the one difference. In the middle of these models, especially a variational autoencoder, there's a latent space. A low-dimensional space. It's a type of dimensionality reduction. You put a piece of data in through an encoder, gets down to a latent space, which is some sort of low-dimensional representation. Then you're going to put it out through a decoder and get something that statistically matches back on the other side.

Paul Middlebrooks
We have to sample from the right place in the latent space to get the right-- I guess--

Chris Rozell
That's what you train. That's part of the training to match the statistics of the data, is to construct that latent space. Now, you have this latent space. One could imagine taking a piece of brain data, going through the encoder to the latent space, and now each dimension of the latent space, you could move that data point essentially. Then you could reconstruct it and you could see what changed. Those latent dimensions don't have names, they don't have labels, but they're dials that you could turn back and forth.

The one thing that we did differently in the training was we said let's train this variational autoencoder to produce statistically indistinguishable brain data, but one of those dimensions in that latent space, we're going to ask it to do a special job beyond just helping to capture the statistics of the brain data. We're actually going to tie it to the output of that black box classifier.

Think about it this way. This generative model is just able to spit out essentially an infinite number of fake brain data, synthetic brain data. Each one of those, we're going to put through the classifier. The classifier is going to say, that one looked sick to me. That one looked well to me. Now that signal, we pull back into the training of the variational autoencoder of the generative model. We ask that one special dimension to account for that decision.

Now what we end up with in the training, take a piece of brain data, put it through the encoder, get into the latent space. If we then move along that one special dimension, what changes about the brain data when we reconstruct it through the decoder is something that will change that classifier's mind about whether that brain was sick or well. You put in a sick piece of brain data, you turn that one dial.

Essentially the generative model is saying, how do I have to change this to make it look more like a well brain? Just like asking your ChatGPT or something, make this piece of text sound more professional. Except we were doing this not through a text input, but right in the latent space. How do we make this brain look more well? The other dimensions, if you were to change them would change something about the brain data, but in ways that didn't change the classifiers.

Paul Middlebrooks
Orthogonal to the wellness metric.

Chris Rozell
Yes. In technical terms, we might call those invariant dimensions because the classifier doesn't care about them at all. Now the biomarker that we actually use is that latent dimension. We can throw that black box classifier away. If we want to, we can even throw the decoder of the generative model away. We can just put the brain data through the encoder, get to that one dimension and see where we're at on that axis. That's our biomarker.

Paul Middlebrooks
You have, let's say 0 to 10 or whatever. The biomarker can be at nine, it can be at one. That's the predictive component that tells you whether you're sick or healthy.

Chris Rozell
Essentially asking, what is the probability that this is a sick brain versus a well brain. That gives us the ability, because we do have the decoder, if we want it, we can turn that dial and look to see what changes. That gives us an ability to visualize and say, as we were talking about at the beginning of this conversation, oh, it looks like this beta band signal has to increase, in some relative proportion to this other signal-

Paul Middlebrooks
So cool.

Chris Rozell
-and this other signal. We can actually see, because it's a generative model, we can see what's changing that would change the black box's mind about whether it was a sick brain versus a well brain at that point in time.

Paul Middlebrooks
This would not have been possible without modern AI.

Chris Rozell
I think not in the way we were able to do it. That both helps performance a little bit, but also gave us the ability to see what was happening. If you think without the modern machine learning tools, we would have had to guess what the right feature was out of all the possible things. Remember, we're not talking about individual features. It's not just, oh, beta band change, or the other thing changed. As far as we know right now, it's a composite signal, it's relative changes happening across different bands. Perhaps--

Paul Middlebrooks
You'd have to exhaustively check all permutations of those features too, right?

Chris Rozell
Exactly. Perhaps some subset of those will work out to be operational and useful all by itself. That would certainly make life a lot easier for the devices that we're using. At least for right now, we didn't know what to look for. A data driven approach, given the important clinical definition of what it was we were trying to look for, let the data speak to if anything, and then what is changing in the data.

Paul Middlebrooks
So cool. That's such a cool setup. Two-part question. I know the answer, but I want you to elaborate. Is this a super exciting time? The second part of the question, is this a super exciting time for these kinds of treatments and understanding how they work, et cetera, and the potential for, are we on the cusp of solving lots of these complex mental phenomenal disorders? The second part of the question is what are, what's holding you back right now? What are the obstacles to that?

Chris Rozell
Those are great questions. I'm very excited about the time that we're in right now. I think we're seeing, early glimpses of what a future can be. There are exciting things happening. I love the research that we're doing. I'm also seeing that companies, like in this case, Abbott Neuromodulation is starting an industry-sponsored randomized controlled trial that could eventually lead to this type of therapy being an approved therapy and accessible to people outside of investigational studies.

Our partner, Medtronic, continues to invest in the technology that would be important for doing these sorts of things. I think it's a really remarkable time, even though those technologies, you might think of as being crude, single channels of stimulation and recording. There are a lot of dreams in the neurotech industry space of going to higher resolution. Of course, I'm sure people are following the BCI sort of advances where many more channels of recording are being made possible in new techniques and technologies.

Paul Middlebrooks
You've shown you could do so much with so little.

Chris Rozell
Exactly. This would be a really great question for the field. We can do an enormous amount with low resolution. Higher resolution is coming online. How do we use that? Is that helpful? It's a question we get all the time. I think until we're able to collect that data, we're not going to know. Perhaps we could do something really remarkable if we had thousands of channels of recording. Perhaps the answer is, this is a global mood state and really one channel is sufficient to capture what's going on and get people healthy, and anything other than that's overkill. We don't know yet because we've never been able to really collect that data.

I think it's a very, very exciting time, from a technology perspective and from a scientific perspective with what we've come to understand over the last decade. Of course, I'd be remiss to not mention that it's also a terribly troubling time with the public conversation about science and research and how and where that should be happening, and how and where that should be supported. I, like many of my colleagues, are concerned that the decades of support that have led to the innovation that we're enjoying today, and that's cures for diseases, that is economic return on investment, that is the building of a workforce that can go into the nascent neurotech industry that's just exploding right now.

There's certainly a lot of concern, and I think rightfully so, that that future may not exist in the way that we've benefited from over the past decades. We'll see what reality emerges over the next few years, but certainly the anxiety around that is already affecting things. I'm already seeing fewer people moving into training programs, fewer people coming to the United States to be part of our training environment here, which really helps us all.

If you want to ask what's holding us back, we're human beings. We only have so many hours in the day. These types of studies are very complicated to do. They take quite a long time to even collect small amounts of data. It's very expensive, and so it needs both the financial and the infrastructure support to do that. I would say the broader picture here is it's not just about one lab or one type of study. It's a really important time for us as a scientific community to communicate to the general public about why what we're doing has value. There are many ways to do that, and certainly your podcast here is an enormous point of light in that need in the world. Then as a general public, we have to decide, what value every different activity we could do has and how we want to put money and time and resources behind it. I hope that science and research is something that has broad agreement is valuable for us as a humanity to engage in. That's a conversation that society is going to have to have.

Paul Middlebrooks

I can tell you, I immensely enjoyed my time at the InterfaceNeuro Conference that you put on at Georgia Tech. Being there, and then a few weeks later, being at this neuroAI workshop that Sean Escola put on, the sense of excitement is palpable in those arenas. It's coming from the basic research work that I do. That milieu, it was almost jarring, the level of optimism and contentment of people with what's going on and the possibilities. That's really exciting. From that outsider perspective, it seems fresh and new and exciting. I'm excited for you.

Chris Rozell
Got a lot of wonderful feedback about that meeting. Thanks for bringing it up. I'll say InterfaceNeuro is a meeting that Rice University, their neuro engineering group started a few years ago, and we worked on hosting a version of it here this year, they'll be hosting it next year. It's a really wonderful meeting that brings science and technology and clinic, lived experience, voices, and industry all together. It's been a privilege to be part of that. One of the best comments I felt like I got was I felt optimism there in a way that I haven't in a long time.

Paul Middlebrooks
I was going to make the terrible joke that me and my colleagues probably need your DBS treatment. You guys don't need it, perhaps. I'm making light of a serious condition.

Chris Rozell
I'll say, I feel that optimism. I could not be more excited about what the future can hold for us all. Everyone comes to feelings like that for different reasons. For me, just very myopically in our own life, seeing a life transformed is a really powerful thought. It really reorients a sense of purpose for you and a sense of what could be possible.

Paul Middlebrooks
That was one of the most powerful things that at that workshop that you put on is you talked about the lived experiences of patients, and you had multiple patients come on stage and share their lived experiences, which was just a treat and really makes things concrete. Deserving of optimism and feeling excited, I think.

Chris Rozell
I was very proud of that and work together with partners in the neurotech space that helped make that possible. Specifically Blackrock Neurotech and Medtronic really came alongside us and partnered. If people want to hear that, some of those stories have actually just been released in a podcast from The Story Collider. It's an episode called Wired Lives. This were people with either deep brain stimulation implants for Parkinson's, for epilepsy, or people with brain computer interfaces, so some of the BCI pioneers that were in the early research studies or continue to be in research studies. They came on stage, told their personal stories. Now I think just about a week ago, was released as an episode called Wired Lives from The Story Collider podcast.

Paul Middlebrooks
I'll link to that in the show notes. Also, people can just search it up also. We don't have a ton of time here. You told me a story at breakfast, [clears throat] excuse me, about a month ago, one of these workshops. We don't have hours and hours here, which I'm sure you could spend talking about this. You come from a non-affluent background in Michigan, like we said, apparently playing hockey.

Chris Rozell
Didn’t play, I was a fan.

Paul Middlebrooks
All right, big fan. These days, you just became the inaugural director for the new, what's called the Institute for Neuroscience, Neurotechnology, and Society at Georgia Tech. Congratulations.

Chris Rozell
Thank you.

Paul Middlebrooks
I don't know where we should start here. I also want to know how your job is going to differ now than just running a lab and doing all the research that you did, how the nature of your job will differ. One of the things that you communicated to me was how important it is to you to help people around you, and to form collaborations and to lift other researchers up, and to communicate what you're doing to society. You gave me the reasons for why you feel that way. I was hoping that you would share those reasons with me and with the audience.

Chris Rozell
Happy to. As you mentioned, I grew up in a fairly rural area in Michigan, a place where it's not always common or expected that people are going to go on to college or go on to scientific careers. I'm not sure I knew scientist was a career one could have growing up. First generation to go to college in my family.

Paul Middlebrooks
You don't hear that much anymore.

Chris Rozell

Yes. That was true. Grew up in a place where I saw people that were in difficult circumstances. My grandmother's a member of the local Native American tribe there. Certainly saw difficult circumstances to break out of, and was fortunate that there were people around me that saw a talented kid that they wanted to help get opportunities, but didn't really know what those opportunities should be.

I think part of my story to convey is that I had no idea what I was doing. I stumbled. I don't want to say wrong terms, because I think that are all valuable, but I did not take a straight line to what I'm doing. I went to college, I checked the box that said computer engineering, because people told me I was going to be an engineer. I had played with the computer a few times and thought it was cool. Those words together, no idea what it meant, but I'll check that box.

Paul Middlebrooks
At that time, did you have ambition? Were you driven? Were people just telling you how smart you were and you thought, this is what I'm supposed to do? That's what happened to me. I didn't have an ambition. I did it because that was the story people told me about myself.

Chris Rozell
I don't know that I had a specific vision or ambition. There was a lot of that, people telling you that you're good at something and you should do it. I think that there's a certain amount of when you see that you're good at something, you lean into that because it helps you feel good. I grew up in a farming family and blue collar jobs where hard work is just how you survive. I grew up in a way that your default mode is you put your head down and just work as hard as you can at something. Ambitious in that sense that I felt like, I want to go do something.

Paul Middlebrooks
That's how you get it done.

Chris Rozell
It wasn't a specific vision. I would have told you that I wanted to go design computers or something, but I didn't do like that. I went to college. Again, just picking a place, I ended up at the University of Michigan, which was an amazing choice, but it wasn't a very informed choice. I went because I had a few friends that I happened to know that were there. They had a marching band that looked like it would be a lot of fun to be in. I did a lot of arts and performing work.

I ended up auditioning for the music school there my second year. I ended up doing a dual degree in music and engineering and ended up being there six years. That was fortuitous because I was still figuring out who I was. It was a time of newness where I was meeting people from all over the world. I had been just in this one rural region.

Paul Middlebrooks
You didn't travel much.

Chris Rozell
No, not at all. I had only ever been a few hours away from where I grew up. It was eye-opening to me to be around people that were different than me. At the same time, there was a level of familiarity and comfort that I hadn't quite experienced before because it was a lot of people that were-- they were thinking about thinking for a living and these kind of careers in science and engineering and things that I just hadn't been exposed to.

It was this disorienting time where it felt both very foreign and comfortable and familiar in a way that I hadn't experienced. That time was valuable for me to figure out something about who I was. As a practical matter, let me start doing research and start teaching for the first time because those last couple of years, just from a credit hours perspective, slowed down quite a bit, and so it created space for some new experiences.

Paul Middlebrooks
You're teaching as an undergrad?

Chris Rozell
After four years I had essentially finished my engineering degree. I was just working on the music degree. The engineering school essentially let me be a TA for one of their low-level classes. It was a transformative experience for me. I went through this time thinking a research career might be what I wanted to do. I didn't really know much about research, but I knew it was essentially a prerequisite to be a professor at a good place.

Paul Middlebrooks
You didn't know that it entailed thinking for-- you mentioned the thinking part, but that that would be-- it's part of a draw. Is you get to be creative and solve problems, solve hard problems cognitively.

Chris Rozell
I'll say I feel that way now. At the time, I would have said that is a necessary component to be teaching at a major university, and that's really what I want to be doing.

Paul Middlebrooks

The teaching part or the being a professor part, being called being a professor part?

Chris Rozell
Being a professor part, but mostly I thought of the teaching when I thought back. There was something very gratifying, and that's tied into I was a camp counselor for many years, so I was seeing the impact you could have investing in young people's lives. These things were coming together, the ability to invest in people, the technical aspects that were very cool to be a part of. The educational aspects. I did not yet have the spark for the creativity through the research really driving me.

I was saying, I think the questions that are most interesting are probably ones related to the brain. At the time it was really sensory perception was really driving me. You can imagine through the music degree. I said, I don't think I can understand that by studying music. I think I need to understand the brain, but I'm obviously not going to go be a neuroscience major. I haven't had a biology class since the ninth grade. I'm not on that track, and kind of vocationally an engineer. I wonder if I could use these tools of engineering to study the brain.

It was a long time ago. That was not a common track, but I was able to find a few people, including the person I ended up studying with, Don Johnson, that was a card-carrying engineer. Don was at Rice and had really been an electrophysiologist while an electrical engineer, and then had essentially become one of the early generation of computational neuroscientists. Ended up going to work with him, being surrounded by all this incredible engineering talent, could take the neuroscience classes from the medical center across the street at Rice and get this really rich interdisciplinary mix of the neuroscience, the engineering tools, coming from this arts background that I think just broadened my perspective.

It wasn't intentional, but I think I stumbled through this path that has combined this milieu together that has ultimately been beneficial for me to be able to think about what creativity means in the context of research and how to give and take feedback, and all the things that you learn as an artist and mixing it together with the science and the technology.

Paul Middlebrooks
Is that why you value interdisciplinary approaches so much?

Chris Rozell
100%.

Chris Rozell
It is, my major parts of my personality have been forged in ensemble work. I've never fit in this mold of a single PI, with their single R01 doing their own work. That's always felt like an uncomfortable stance to me. Certainly a lot of people warned me that that's not a way to build an effective career.

Paul Middlebrooks
Why? Because you're going to be 1 of 100 authors on every paper or--

Chris Rozell
If you aren't going to own a space and [crosstalk] depth in that one space and be known as the expert in that space, it can be difficult to succeed. I don't want to minimize the real challenges with that, but I think that was never a comfortable posture for me to take. I always felt more comfortable and think that my skills really are best suited to trying to bring different areas together and translate languages across areas. It's just something I've developed a fluency for. If I was going to do this job, I think the only way that it felt good to me was to try and sit in these interdisciplinary spaces. If I couldn't be successful with it, I couldn't be successful.

Paul Middlebrooks
Do the job of running a lab?

Chris Rozell
Yes. I don't think I knew another way to try and do it that felt quite natural to me. That was the journey that I started out on, in theoretical neuroscience and really thinking about sensory systems through building some technological tools and then wanting to have more applied impact, for a number of reasons, including seeing the effect of neurologic disorders in my own family brought me to wanting to think about the clinic, and through an interdisciplinary meeting of clinical colleagues up the road at Emory, with the engineering colleagues here, we were trying to drive those interactions, and found myself in conversations that felt really resonant and felt like we had something to bring and to offer.

Paul Middlebrooks
That's cool.

Chris Rozell
Especially in the space of psychiatry. I think that's a whirlwind tour through it, but it is why I feel so passionately about-- the thing that we're trying to do here is so complicated that it's bigger than any one of us. It's bigger than any one thing that we can hold in our own expertise. Bringing together scientists of different stripes, engineers of different stripes, clinicians of different stripes, the lived experience voices, the magic for me happens where all that comes together.

I know it's not the typical path for a professor, but I've come to love the research part of it in a way that it was not the spark that started me. Even when I started as a professor, I would still say I enjoyed the research, but it was part of a milieu here. While I still enjoy teaching, I love teaching, I think that I've grown into a space where the creativity and the impact that we've been able to see through the research, and especially through the interdisciplinary part of it, is what's really animating to me.

Paul Middlebrooks
We skipped over your grad school days along your path here. You had mentioned to me that there were some challenges along the way there, as-- I don't know a graduate student or someone who obtained their PhD who does not have war stories from their graduate studies, or questioned whether they wanted to continue existing, whether they wanted to continue the program, et cetera. You mentioned you had some that made you question your choices. What was going on there?

Chris Rozell
Absolutely. I'm glad you brought that up because I skipped over it in the story and that was probably an oversight because I think it's a really important story to tell. We see these very polished biosketches and CVs of people and it looks like it was a linear path. It's often not. I've always admired, the folks that have the shadow CV up where they write every grant that they applied for that they got a rejected--

Paul Middlebrooks
Oh, that's cool.

Chris Rozell
You're right. Grad school was a particularly difficult time for me. Maybe one of the darkest periods of my life, because it was a time where-- maybe the first time that I wasn't succeeding at what I was doing. It was a time where I had a very specific notion of what was coming next. I had this dream of becoming a professor and was day by day seeing that slip away.

Paul Middlebrooks
Because you felt like you were failing or--?

Chris Rozell
Not felt like, I was. I was not thriving. There are a number of reasons for that. One, technically I was not the strongest in the program. That's just a objective fact. I have other skills that aren't measured on tests, but I technically was not particularly strong. It was also so new to me and the environment was so foreign that I just wasn't making progress. My specific issue was we had these very abstracted ideas, but I was having trouble turning them into concrete research questions and just felt stuck.

My advisor, who is wonderful and I have a great relationship with, and I love him, he's hugely influential to me, he didn't know how to get me unstuck from that. I was just sitting. I would come home to my wife, I was newly married at the time, I would say, I didn't do anything today. She would say very graciously, you just don't see the value in what you're doing yet. That would become apparent with time. You just have to stick with it.

Paul Middlebrooks
You mean you didn't accomplish anything today, not you didn't—

Chris Rozell
I would correct her and say, you didn't hear me right. I didn't do anything today. I stared at the wall of my office for seven hours because I didn't know what to do.

Paul Middlebrooks
Oh, that's crushing.

Chris Rozell
I almost left the program. I remember going and sitting in the office of my closest friend there and saying, I'm not sure how much longer I can do this. It was very dark. I think it's an important part of the story to tell. I ended up in a cardiologist's office at something like 24 years old with him saying, what are you doing here? With essentially health trouble that I had induced myself through the stress that I was feeling. It was clear it was damaging my young marriage at the time. It was damaging me. There had to be a major reset.

There were a number of things that helped. One was I brought more mentors into my circle, both at Rice and beyond. People like Rich Baraniuk and Bruno Olshausen, a theoretical neuroscientist that I would eventually postdoc with before I came here. I had to be forceful, not because they weren't willing, but everyone's just very busy. I essentially sat down in Rich's office one day and wouldn't leave until he wrote to Bruno, who I didn't know at the time, and invited him out to visit because I didn't know what else to do. Through widening that circle, I think it let me see the parts that I wasn't learning.

I had to see this process of formulating a research question one time. I had to see it executed one time up close. Then something clicked. Then I could do it. Somehow, I wasn't getting that from where I was sitting. By expanding my mentorship circle, I was. I know a lot of people, if they have trouble in grad school, is oh, I had a terrible advisor or the environment wasn't great. I was blessed. It was an amazing environment, amazing mentors. I was just stuck in some attractor that I couldn't get out of.

I had a wonderful support system of friends and family. My wife, Kara, is an angel sent here to earth to protect me from myself. She had a really shrewd piece of advice, which is, "Would you sit down and write a mission statement for yourself? Not what job do you want to have, but what are you about?" I did that. It was actually a very freeing exercise because it let me step away and say I have this vision of what my career is going to be. That may or may not happen, but I've articulated what I'm about. No matter how that career works out, I can still be about those things. I might have to find a different career path to express those things. Maybe it's a collection of different ways through volunteer or different careers that I can do those things.

Paul Middlebrooks
That was a central identity that you could come back to.

Chris Rozell
It was. You could make decisions from. It was very comforting to be able to separate my success on a particular career track with my own identity. To basically separate my identity from my professional success. Then I could be much more rational about it. I could say, listen, I grew up in a certain way. I know what bottom looks like. I'm educated. I'm employable. My family's not going to go hungry. I can take care of my basic needs, which wasn't always a given for me. I know what I'm about. I can lean into these things in many different career paths.

This one career path is still my aspiration, but I know that I can still be about who I am. That was one of the greatest gifts that my wife has given me, in addition to just the grace of sitting with me in that time that was so difficult. It was free in a way that just unlocked something for me. I was glad to be able to navigate out of that time. I was glad to be able to see that my skill set is actually better suited for this job than it is for the job of being a grad student.

Paul Middlebrooks
That's odd. You got through the—

Chris Rozell
I know. I know that that's not most--

Paul Middlebrooks
It's usually opposite.

Chris Rozell
I know. I think that is true for me. I'm better in this role than I was as a graduate student. It let me see that that was going to be the case. It let me, again, divorce my identity from what I'm doing, which has been a helpful skill in this job, because these are jobs that can really eat you up. They will take every amount of time and energy that you can give them. Being able to draw boundaries around the job has been an important part of trying to stay healthy in it. Using a rooting of my identity in something that's not my professional success, or at least I'm imperfect at it, but that's my aspiration and that's my goal, and that has been part of the toolbox that I've tried to use to keep healthy through a career of this job, which can be quite hard.

Paul Middlebrooks
All right, Chris, I know we're up against the limit here. I know that you have a hard out, but thank you for sharing that personal story and your personal stories along your journey. Thanks for sharing. Also, the research. Congratulations on the new position. We did not get to talk about Neuromatch, which I will link to in the show notes, and people can learn more about. Hopefully we can talk about that another time. Hopefully we can share another breakfast sometime at another workshop somewhere. Anyway, thank you for coming on. It's been a pleasure talking.

Chris Rozell
Thank you, Paul. It's a privilege to be here. Thank you again for all the work you're doing, trying to bring light in the world to what's happening in the science and research world. It's a great thing that you're doing. It's a privilege to be here. Thank you.

[music]

Paul Middlebrooks
“Brain Inspired” is powered by *The Transmitter*, an online publication that aims to deliver useful information, insights, and tools to build bridges across neuroscience and advanced research. Visit thetransmitter.org to explore the latest neuroscience news and perspectives written by journalists and scientists. If you value “Brain Inspired,” support it through Patreon, to access full length episodes, join our discord community, and even influence who I invite to the podcast. Go to braininspired.co to learn more. The music you hear is a little slow jazzy blues performed by my friend, Kyle Donovan. Thank you for your support. See you next time.

[music]

Subscribe to “Brain Inspired” to receive alerts every time a new podcast episode is released.