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Gemma Ware: Welcome to The Conversation Weekly. I’m Gemma Ware in London.

Dan Merino: I’m Dan Merino in San Francisco, and this week we’ve been learning about how advances in technology and neuroscience are leading to some real breakthroughs in the way doctors can treat people with a variety of mental illnesses.

Moksha Patel: I first developed symptoms of OCD starting when I was very young, four or five years of age. I was officially diagnosed in high school in around 2007, and OCD was really taking over my life. The most obvious of my symptoms were not being able to use any public restrooms, showering for an hour after using the restrooms each time. Using chemical cleaners on my skin and my mouth. I wouldn’t eat or drink despite working 12-, 15-, 28-hour shifts in an attempt to not to have use the restrooms.

Dan Merino: This is Moksha Patel. He’s an assistant professor at the University of Colorado in the United States working in the Division of Hospital Medicine, but today we’re not talking to him in his capacity as a physician. Instead, we’re talking to him about a new treatment he’s recently undergone for his OCD.

Moksha Patel: What happens with OCD is people get recurrent or intrusive and unwanted thoughts. And these thoughts cause immense distress. And so you perform a ritual or compulsion in order to try to decrease that distress. Lo and behold, it doesn’t work and it just reinforces the fear cycle. It really feels like you’re trapped in a prison within your mind, a prison of anxiety. We as patients with OCD will start reflexively just sensing danger.

And so, let me give you an example. I could be driving on the street and in my rearview mirror, I can see a pedestrian walking well on the sidewalk, I’m well two lanes to the left of him. And my immediate connection in my brain is, well, what if you hit that pedestrian?

Dan Merino: Hmm.

Moksha Patel: And visually I can see the pedestrian still walking, but that unwanted thought comes up like, well, but what if you’re just, you know, what if you’re not seeing it correctly? What if he’s, you just clipped him and he’s hurt, and what if you hurt him? And so that kind of danger signal, whereas I think most people drive by, take a look at the mirror and say, oh, okay,
there’s a pedestrian. Make sure I stay in my lane. But that dangerous signal of, oh no, what if I hit him?

**Dan Merino:** After his diagnosis in 2007, Moksha sought treatment from more than a dozen therapists and specialists, but nothing worked. Eventually, his supervisors at medical school noticed that he was struggling and introduced him to a researcher at the University of Colorado, Rachel Davis.

**Rachel Davis:** So I’m Rachel Davis. I’m a psychiatrist at the University of Colorado Anschutz School of Medicine.

**Dan Merino:** Rachel worked with Moksha for over a year, trying various combinations of medications and exposure therapy. But when she saw that none of these traditional forms of treatment were really helping Moksha with his severe symptoms, she suggested he might be a good candidate for what is called deep brain stimulation. This changed Moksha’s life.

**Moksha Patel:** From a practical standpoint, after the DBS, I can now eat and drink freely. I had a falafel plate for lunch today, had some chai. I can use the restrooms freely at work. Having that freedom has just been so life-changing for me to open up doors to be able to travel, to be able to eat.

**Dan Merino:** Tell me what it was like when you guys first turned on the electrodes and then Rachel, you started kind of playing with these settings. What was that moment like?

**Moksha Patel:** So I’ll say it depends on the settings. There’s hundreds, probably thousands of different settings that you could do when you tried changing every little variable. Some settings. I felt elated. I felt like I could conquer the world. Other settings, I was very anxious, very depressed. So it was a spectrum. But when we found the settings that were most suitable for me, I’ll tell you, it almost felt like that prison wall had broken down.

**Gemma Ware:** This is amazing. This has completely changed his life. I mean, what a dramatic turnaround.

**Dan Merino:** And all because there’s a couple electrodes in his brain. It’s pretty wild.

**Gemma Ware:** So this deep brain stimulation, I’ve heard about this, but mainly is something to treat Parkinson’s. Is that the same kind of technique that’s being used on Moksha?

**Dan Merino:** Yes, it’s the same basic ideas. Moksha’s got some electrodes implanted in his brain, they produce little electrical pulses and when those electrodes are doing their thing, OCD is far less severe.
Gemma Ware: I never really thought that OCD could be treated with something like that, something so physical, like a brain implant. It kind of reminds me of, say, a lobotomy, something from like the 50’s or 60’s or something quite dramatic.

Dan Merino: It does sound a bit like that, and in a weird way that we’re gonna get into in this episode. It is. Sort of based on similar principles. But it’s very different, right? Like, lobotomies were obviously a terrible, destructive thing. As I’ve been doing the interviews for this episode, Gemma, what I’ve been really learning is that it seems like we’re at a bit of an inflection point when it comes to treatments for mental illness. The combination of ever-increasing knowledge about how the brain functions with advances in technology is opening up a new era of treatment, and some of it is going back to similar principles doctors were trying on patients like 75 years ago.

Gemma Ware: So it’s interesting that we are revisiting these ideas from such a long time ago, but how is that affecting patients today?

Dan Merino: Well, what it means is that patients with depression and addiction and, like Moksha, OCD, are really beginning to get access to new, although I guess kind of old, treatments that can help them in really meaningful ways. And an important part of this is that in addition to incredible benefits that patients are getting, every time these new types of treatments are done, we’re learning a lot about how the brain functions and what’s going on with disorders of the brain.

Gemma Ware: It’s always a journey with the brain, I know that. So how did we get here? How does this actually work? And like, where are we going? I guess I’ve got so many questions.

Dan Merino: Well, it goes back a long way. And the first people to think about using electrical currents to treat mental illness were, like, believe it or not, the ancient Greeks, they were putting electric yields up to people’s heads. I don’t think they quite knew what was going on, but, you know, ballpark, right? But science has obviously come a long way since then.

So to help us understand the history of modern neuroscience and how we got to putting electrodes back in people’s brains, I called up Joseph Finns, a neuroethicist and professor of medicine at Weill Cornell Medical College, part of Cornell University in the US. He started by pointing out the types of treatments for mental illness, — things like drugs versus therapy versus physical interventions like deep brain stimulation — were all seen as belonging to the same discipline.

Joseph Finns: Paradoxically, in the beginning of the last century, psychiatry and neurology, such as they were, were, were pretty unified. They started in the same place. Freud himself was trained as a neurologist and then went on to discover psychoanalysis.
**Dan Merino:** Sure.

**Joseph Finns:** But with the advent of psychoanalysis and more psychological theories of the brain, you started getting different kind of camps between what was called the somatic therapies, you know, in psychiatry — like electroshock therapy, insulin therapy, lobotomy, for example, being the most egregious of that. And then on the other side, you had psychoanalysis and more psychological approaches. And you began to get this split, who did what? So most therapy is provided by non-physicians, there were psychologists, social workers, counselors, and so we had that split. I think what’s happening now is that we’re returning back to a convergence, where neurology and psychiatry and psychology are all speaking to each other in a way that is more holistic.

**Dan Merino:** The idea of using electricity to treat mental illness started making waves amongst the neuroscience community in the middle of the 20th century, in large part thanks to a man named Jose Manuel Rodriguez Delgado, professor of neuropsychology at Yale.

**Joseph Finns:** Delgado was famous because in 1964 he was on the front page of the New York Times because he put a thing called the stimoceiver, a deep brain stimulator into the brain of a charging bull in a bullring outside of Cordova in Spain. And he was able with an electrical current, by radio frequency, to stop the bull in his path. And I think, you know, he’s often clumped with Walter Friedman as a somatic therapy. But if you actually read his correspondence and his thinking later in life and also during this actual period, he got interested in the electrical stimulation of the brain because he was horrified by lobotomy. And he wondered, was there another way of achieving those effects with electrical stimulation of the brain, which didn’t destroy the brain, versus the ablative or the destructive interventions of psychosurgery, which indeed destroyed the brain.

**Dan Merino:** Did you talk about an interesting era, right? The somatic era of neuroscience where we’re doing lesioning, we’re doing lobotomies. What did we learn from that era and why did we stop?

**Joseph Finns:** I think there are lots of theories. It stopped because these new drugs replaced it.

**Dan Merino:** Hmm.

**Joseph Finns:** It was a less invasive way of quieting, as it were. I mean, the effect of the lobotomy was to dampen out and quiet people, and I’m not endorsing it, I, it was an egregious procedure —

**Dan Merino:** Sure, of course.
Joseph Finns: But it took away symptoms, and took away from people’s personhood, took away from their excitability and, and all kinds of things. And there was a less aggressive way that was reversible with drugs. So it was replaced by something that was less toxic and more effective —

Dan Merino: Mm-hmm.

Joseph Finns: and net-net was better. So psychosurgery and this sort of somatic therapies began to fall out of favor because of the rise of psycho-pharmacology. And these were drugs that had a really dramatic effect on the psychoses, and then that led to a whole era of pharmacologic intervention.

Dan Merino: Delgado himself was also experimenting with electroencephalography to explore the effect of thorazine, the first anti-psychotic drug used to treat schizophrenia. A lot of the drugs discovered in the forties and fifties and sixties, including thorazine, are still in use today, and while there has been a lot of progress in terms of how much we understand about the brain and how it works, as well as the development of a lot of new drugs, there hasn’t been a lot of progress made on physical interventions that can be used to treat mental illness. So deep brain stimulation is, in a sense, a return to old ideas, but using vastly more modern technology.

Joseph Finns: History doesn’t repeat itself, it rhymes, right? And now we’re hearing a rhyme in the sense that that deep brain stimulation, in a way, is reminiscent of the work that Delgado was pursuing mid-century, with less knowledge of the brain and with more primitive technology.

Gemma Ware: Dan, brain surgery to treat mental illness seems like a fairly dramatic solution at any time. But back then in the fifties when they were using quite primitive technology — that’s really scary. So the principles we’re using today are similar. So what’s changed in terms of the technology between then and now?

Dan Merino: Well, the biggest change has been in brain imaging. Starting in the 1920s, we got EEGs, a electroencephalograms, which just show an output of wavy lines that indicate brain activity.

Gemma Ware: Mm-hmm.

Dan Merino: Then in the 1970s, we got computed tomography or CT scans. These take a cross-sectional x-ray image of the brain.

Gemma Ware: Okay. I’ve heard of them.

Dan Merino: In the nineties, there was a really big breakthrough for neuroscience with the development of fMRIs, functional Magnetic Resonance Imaging. These allow you to see what
parts of the brain are active when somebody does something or hears something, or there’s activity in the brain. And most recently, there have been advances in what is called diffusion tensor imaging, and this, crucially, allows researchers to see the interconnected fibers that make up the circuits of the brain.

**Gemma Ware:** Hmm. Okay. That’s all looking at the brain, though, and I know it’s clearly given researchers a better understanding of how the brain functions, but there’s a big difference between being able to see what’s going on and actually take pictures of it and inserting the electrodes, implants into the brain. So why did neuroscientists think that doing that might be a good thing to try again?

**Dan Merino:** This is actually a really interesting story, and one that gets at what seems to be kind of a rule of neuroscience and treatment of mental disorders, as it’s a lot of trial and error. The brain is so complicated, when people try to introduce a new treatment, they end up discovering a lot of things about the brain that they weren’t necessarily expecting to find.

**Gemma Ware:** Hmm.

**Dan Merino:** And that’s exactly what happened with deep brain stimulation; In 1987, some doctors were trying to treat a patient with Parkinson’s with an old method and discovered something unexpected.

**Joseph Finns:** With Parkinson’s, the story was Alim Benabid, who won the Lasker Prize with Mahlon DeLong for his discovery of the mechanism of Parkinson’s disease, he was going to do an ablative surgery — that is, actually burn a little area in those connecting structures in the brain that helped to smooth out movement. And when he did the ablation before they burn it, they stimulate it to make sure they’re in the right place.

**Dan Merino:** Sure.

**Joseph Finns:** And he stimulated this area, and he noted the person’s tremor went away. So it was serendipity. And he said, well, maybe I don’t have to burn a lesion in this area. Maybe I could stimulate this area instead. And that led to deep brain stimulation for Parkinson’s disease.

**Dan Merino:** Well, it’s interesting you mentioned this idea like, you know, it was happenstance, right? This discovery of the mechanism for treating Parkinson’s — and this is kind of something I’ve been trying to wrap my head around and figuring out how to describe well — it seems that because of how complicated the brain is, a lot of this stuff almost happens that, we know this treatment works, we don’t quite know why. And that is this back and forth between the treatments push our understanding of the brain, which pushes our treatments of the brain.

**Joseph Finns:** Right, right.
Dan Merino: And it’s kind of this upward stepping.

Joseph Finns: Well, that’s why we have to always be humble

Dan Merino: Hmm.

Joseph Finns: when we describe something, because it’s likely that it’s gonna be wrong in, in a decade or two or a hundred years from now. So it’s all iterative. If you talk to Benabid, and I’ve heard him speak and you know, he’s not sure if it’s stimulatory or inhibitory. In other words, depending on what part of a circuit, you know, it’s hard to know whether you’re having a positive effect, which is positive or a negative effect on a negative effect could be a positive.

Gemma Ware: Hold up a minute here, Dan. I’m really not sure I get this. There’s a lot of double negatives going on there.

Dan Merino: It’s really complicated because the brain is complicated, right? And that’s like part of the whole question here. So just lift your hand up off your desk, Gemma, and hold it. Not moving…

Gemma Ware: Okay.

Dan Merino: Right now, your brain is sending signals through your neurons that are telling you to lift your hand.

Gemma Ware: Mm-hmm.

Dan Merino: Your brain is also sending signals that are telling you to not move your hand. And then at the same time, there’s other pathways in the brain that would cause you to lift your hand up higher or wave it or wiggle your fingers. And those pathways are not firing right now. So it’s both yes and no; and firing, and not firing all at the same time. And when you’re tweaking things in the brain, it’s hard to tell whether you’re boosting a signal that’s too low, for example, or counteracting a signal that’s too high, or introducing a signal that isn’t there and really should be.

Gemma Ware: Okay, I think I get it, but it’s still fascinating to me that they don’t really understand why this kind of deep brain stimulation is actually having the effect that it has on people with Parkinson’s, let alone OCD. So it drives home that point, right, that with the brain, doctors are really just kind of learning as they go along.

Dan Merino: Exactly. And they’re doing more and they’re learning more, and they’re doing more and learning more, and it’s this feedback loop that is really driving forward treatment of mental disorders that are historically very hard to treat. And one of them, as we heard from Moksha, is severe OCD.
Gemma Ware: Yeah, I wanna hear more about Moksha and his treatment, because I can wrap my head around how deep brain stimulation could help someone with Parkinson's because the tremor is like a visible reaction. But with OCD, that’s just harder to imagine. So how does deep brain stimulation actually work to treat OCD?

Dan Merino: Well, let’s let Rachel Davis explain.

Rachel Davis: So what is deep brain stimulation? It involves implantation of electrodes in the deeper areas of the brain, in the ventral capsule ventral striatum, and these electrodes are connected to extension wires, which are tunneled down the skin and connected to pulse generators at chest, which look very much like cardiac pacemakers. And these pulse generators deliver small doses of electrical current to the brain. There’s two main reasons why people thought this might work, and one is the history of brain surgeries that did work for OCD, and the thought was, can we create a functional lesion? Which means, basically, can we have a similar effect by stimulating not destroying tissue if we stimulate those same areas that we destroyed in brain surgery? And then two, because we know that Parkinson’s is also a disorder of neural-circuitry, and we know DBS works in Parkinson’s, people thought to try it in OCD, so it was actually first tried experimentally in OCD in 1999.

Dan Merino: Since the first trial, there’s been a lot of technological advancements in the electrodes themselves and how they’re controlled and also on where they’re placed in the brain. But the actual surgery itself is more or less the same.

Rachel Davis: So, we implant the electrodes and we wait about a month to let the brain heal, but then we turn on stimulation. And it’s a very complicated process of figuring out the right programming settings. That takes place over several hours, over three days. Basically we’re looking to find the settings where the patient feels that their mood is better, their anxiety is less, and that they have more energy. And if they experience those things, then that correlates with improved OCD symptoms down the road. And for some people, that can be improved OCD symptoms within weeks, and for other people, it’s improved OCD symptoms within months. Now, this is different from Parkinson’s. In Parkinson’s, they often do the surgery awake, and you can turn on stimulation during the surgery and immediately see the patient’s tremor go away. And so the difference in OCD is we’re using kind of proxies, right? We’re using indicators that hopefully down the road will be related to a reduction in OCD symptoms.

Dan Merino: So what are you actually changing as you’re tweaking these settings and dialing the electrodes back and forth? Like, what are you actually doing here?

Rachel Davis: We’re changing the voltage, so how strong the current is. We’re changing the frequency, so how frequent or how fast the pulse is, and we’re changing the pulse width, so how long the pulse width is. But I’d say probably the most important thing we’re changing is which
electrodes we’re stimulating. So it’s actually a very thin electrode that has four contacts on it, and you can activate one or all four or two or three of those contacts, and then you can shape the current in different ways. And so by doing that, we’re stimulating slightly different areas of the brain, and what we’re probably doing is trying all sorts of different things until we capture the exact white matter tract that we need.

**Dan Merino:** And white matter tracts are this—?

**Rachel Davis:** So white matter tracts are the areas in the brain that are connected that communicate with each other. It’s, like, where signals travel along. And because we don’t currently have a way of precisely targeting that white matter tract, that’s why we have to do all this trial and error to find out. I wanna kind of give you a visual so it—

**Dan Merino:** Yeah, please.

**Rachel Davis:** You know, Moksha sitting on the couch, me sitting, oh, maybe 10 feet away on a chair with a tablet and I’m programming via Bluetooth.

**Dan Merino:** Huh.

**Rachel Davis:** So, like, I’m making changes on my tablet, which is affecting his brain 10 feet away. And we’re seeing in real time, like, the change. It is, it is remarkable.

**Dan Merino:** Can you sense it when you first got it turned on or the settings were being changed or anything?

**Moksha Patel:** Uh, so physically, no. The brain luckily doesn’t have pain receptors or anything, so it doesn’t feel any of those, uh, physical stuff. You know, one of the cool parts about the programming is, is Dr. Davis can grant me the permission to change between different settings, and there’s multiple reasons to do that. So, yes, I can feel when I’m on my different settings and when my amplitude is higher, when my amplitude is lower, so I can sense that from an emotional/mood/anxiety standpoint.

**Dan Merino:** So why do you have different settings? Just, you know, the brain is a dynamic place and different settings respond to different situations? That’s very fascinating to me.

**Moksha Patel:** Well, I think the reason that we have different settings is there’s a thought that, you know, if you keep stimulating the brain with the same type of pattern, you could develop a habituation or, you know, the effect may decrease. So one of our thoughts is, if we find two settings that do appropriately well, and I change to one of them during sleep time, then theoretically we are less likely to develop that habituation. And I have found that, for example,
my sleep settings, I’m more calm, I’m less energized. But if I was to try to work on those lower amplitudes all day, I think it would be harder.

**Dan Merino:** One of the really interesting things Rachel explained is that this process of programming and adjusting the electrodes, and in fact the new technologies contained within the electrodes, is of course helping Moksha feel better, but it’s also allowing Rachel and her colleagues to learn about the brain in ways they never could before.

**Rachel Davis:** We have electrodes that not only can stimulate, they can record the electrical pattern in the brain.

**Dan Merino:** Oh, wow.

**Rachel Davis:** And so this is allowing us, you know, to record, deep in the brain, what’s going on when someone is experiencing an obsession, when someone is depressed, when someone is, I mean, we can get this, you know, physiological indicator of their emotional state or behavior, which is just fascinating and I think will help us understand more what’s going on in the brain. And so we can put in the programming parameters into this computer program. We can simulate an electrical field and we can see which white matter fibers or which part of the neurocircuitry we’re actually stimulating.

**Dan Merino:** Oh, interesting!

**Rachel Davis:** So we’re learning a lot because of this technology, actually, which I think will then guide other treatments and also help us be more precise in our use of deep brain stimulation.

**Dan Merino:** So deep brain stimulation for OCD is getting better every day as you guys are learning more. But how effective is it now? You guys aren’t the only group doing this, so kind of across the board, on average, what are the results we’re seeing?

**Rachel Davis:** A good response is considered a 35% reduction in OCD symptoms, and we measure that using a standard scale called the Yale Brown Obsessive Compulsive Scale. And Moksha has had about a 55% reduction at this point. The literature shows that on average, about 50 to 70% of people have that 35% reduction. We’ve done surgery on eight patients here at CU Anschutz, and six out of our eight patients have had at least a 35% reduction. So that’s, 75% of our patients have had a good response.

I also think it’s important to understand, you know, what does that mean? What is a 35% reduction in symptoms that might mean someone goes from spending 12 hours per day on OCD symptoms and being unable to leave the house to spending maybe six hours per day on OCD symptoms and being able to go to school with significant support.
**Gemma Ware:** As amazing as all this is, Dan, I kind of need to throw a bit of a wet blanket on it, because deep brain stimulation, I mean it involves brain surgery, so it’s invasive and presumably somewhat dangerous as well. And that doesn’t make it a kind of treatment that’s easily accessible to most people. It’s also a pretty big decision to take to use it to treat mental illness.

**Dan Merino:** This is an excellent point, Gemma, and even more so when we consider that depression, for example, is one of the leading causes of disability worldwide. A good treatment needs to be accessible. And thinking back to what Joe Finn said about why doctors moved away from physical, or what he calls somatic, interventions on the brain in the fifties and sixties, was because those were destructive, invasive, and importantly, irreversible. Deep brain stimulation is much better and definitely way more ethical, but still a very serious thing to do. And everyone I spoke to for this story was very clear that it’s a last resort, only for when people, like Moksha, don’t respond to other treatments like medication and therapy.

**Gemma Ware:** Mm-hmm. So it’s a last resort and it’s also a serious commitment, but it still feels somewhat crude, right? It is, after all, not that different from what this guy Delgado was doing to bulls back in the 1950’s.

**Dan Merino:** The basic mechanism is the same, you are right, but the knowledge of the brain that researchers are using to direct deep brain stimulation is so much more advanced than what we had 75 years ago. We know now that by manipulating certain neural circuits, it’s possible to influence mental illness, right? We didn’t know that. Researchers are also starting to get better ideas of what circuits influence what parts of the brain, thanks to imaging and also information gathered from patients. And when you put these things together, you can start to explore other, less invasive ways of treating mental illness.

**Gemma Ware:** Okay, so what would a less invasive way of using this similar technique be?

**Dan Merino:** One somewhat new method to treat mental illness by influencing neural circuitry is called transcranial magnetic stimulation, or TMS. Jacinta O’Shea is a neuroscientist at the Wellcome Centre for Integrative Neuroimaging at the University of Oxford in the UK, who’s studying TMS.

**Jacinta O’Shea:** So, how it works is that you put a ferromagnetic coil on the scalp, so it’s just a sort of figure of eight shape, and what you do is pass a rapidly changing electrical current through that coil. This is controlled by a machine, and as everyone might remember from their secondary school physics, magnetic fields, when they’re rapidly changing, they generate electrical fields sort of perpendicular to their angle of orientation. And so if you place this ferromagnetic coil on the scalp, it will induce an electric field to pass painlessly through the skull and into the brain tissue underneath.
**Dan Merino:** Depression is one of the illnesses transcranial magnetic stimulation has had the most success in treating, but this approach definitely comes with some limitations.

**Jacinta O'Shea:** What we do know about depression is that much of the neural dysfunction is actually in quite deep, relatively old areas of the brain, by which I mean you find them not just in primates, but in our sort of reptilian areas of the brain that are important for, like, threat detection. And so one limitation of TMS is that you cannot access those deep areas directly. So when we put a TMS coil on the scalp, most of the stimulation is delivered to the first just few centimeters of brain underlying the coil.

**Dan Merino:** The relatively shallow reach compared to something like deep brain stimulation is one of the main challenges facing transcranial magnetic stimulation. So researchers using TMS had to get a little creative with the technology.

**Jacinta O'Shea:** So then the question is, well, how can you get this down to the deep areas where we know a lot of the true dysfunction lies? And the answer is because the brain is multiple different networks that are all connected. So when I apply stimulation to this hub area, it travels along those wires and changes activity in the more remote areas of the brain. One really thorny challenge in treating something like depression is that we know it’s very individually variable. This is true for any sort of treatment approach, including, you know, medications. Medications work extremely well for those people for whom they work, but they may not work well or not at all for other people.

So there’s this question of what’s the right sort of treatment for the right individual. And so, a diagnosis of depression is given when you have a list of certain symptoms for a particular period of time. Somebody else might have the same diagnosis of depression, but have quite a different profile of symptoms. So you might have one person who’s super anxious and agitated all the time and doesn’t eat very much and doesn’t sleep very much. You might have somebody else who’s oversleeping, who’s just got very blunted feelings, maybe overeats, maybe gains a lot of weight. Both of those people might have the same diagnosis of depression, but if we think biologically, is it likely that these two people have the same biological dysfunction? The answer is very likely to be no.

**Dan Merino:** In other words, take two people with the same diagnosis on paper — depression. But they have different symptoms. Chances are, their brains are gonna look very different. So the type of transcranial magnetic stimulation that could help one person with their depression, might not really do all that much for somebody else.

**Jacinta O'Shea:** And one of the challenges in the field is, is depression, can we map that to sort of underlying neurobiological types, let’s say, that would allow us to identify which circuits correspond to which ways of being depressed and therefore might need different types of
interventions? So, simply put, maybe you want to excite these circuits because they’re under-active, maybe you want to suppress those circuits because they’re over-active, as a simple example. And over time, sort of through plasticity changing the activity in those circuits, almost like a sort of circuit breaker, like, trying to break that pattern that’s looping around and around. So that’s kind of one idea about how TMS might be working.

**Dan Merino:** Despite the uncertainty in exactly how disrupting a circuit in a person’s brain can help them overcome mental illness, the early results are looking really promising and seem to apply to a wide range of disorders, too.

**Jacinta O’Shea:** In this particular field, the most exciting thing I think, that has happened in recent years is this new breakthrough treatment with TMS for depression, and this has come out of the lab of Nolan Williams in Stanford, together with Eleanor Cole. They developed this new way of applying TMS, which appears to be incredibly effective. So effective, in fact, that the FDA gave it rapid breakthrough status as a new form of treatment, that it’s so good, they want to get it out there to people ASAP.

And it’s interesting what they did. So, ordinarily when you have a course of TMS treatment, you would come to a hospital, you would have a dose of stimulation every day for perhaps six weeks in a row, say, Monday to Friday for six weeks. They thought, well, can we optimize this? Can we make it more effective?

So they changed it all at once. So what they did was instead of doing six weeks, they squeezed the treatment into five days and you would be stimulated 10 times a day for five days in a row, just at three minutes on the hour, every hour. It was absolutely remarkable the results that they found. In a group of people who were very severely depressed for a very long time, many of them actively suicidal, they agreed to undergo this treatment protocol, and within five days, about 90% of the people were fully recovered from their depression in a way that lasted for several subsequent weeks to months.

**Dan Merino:** Wow.

**Jacinta O’Shea:** the period over which followed them. And they did a proper trial, so a proper placebo arm, which is always very important, and the people who have placebo didn’t show this effect. So, that’s really remarkable. And anecdotally, within 24 hours, the participants were saying, I haven’t felt this good in years. So, that’s amazing. And we don’t quite know how that has worked. There’s a lot of science to unpack exactly what the changes are and so on. But you might say from a patient’s perspective, the important thing is that they’ve been treated really effectively. So that’s really exciting.
Dan Merino: In addition to tweaking the many variables of the actual electromagnetic stimulation itself, Jacinta’s lab in Oxford is also exploring how having a patient do a task or an activity while they’re getting the treatment might increase the effectiveness of the transcranial magnetic stimulation.

Jacinta O’Shea: One of the things that we think is interesting in our lab is looking at how we might make those treatments work more effectively by not just delivering electricity to the brain, but also trying to retrain how people are thinking while they’re having the stimulation. And so our idea is that at the moment, the way stimulation is delivered is a bit like a medication. So you just take your pill, you just receive your electricity, you do that over time and then hopefully things improve.

But our thinking is that maybe the stimulation would work more effectively — and we have good reason to think it would from laboratory experiments — if we got people to switch on and use the circuits that we’re trying to reach with this stimulation. And in particular, if we were able to design forms of cognitive training, mental training, that got people to practice the things that they’re not so good at because they’re affected by the depression. And then if we’re delivering the treatment at the same time, the idea is that we might get a positive interaction between these two things. So from research, we know, like with medication and therapy, at the same time, you have a better outcome than if you just do one or the other.

Dan Merino: TMS is very much still in the early phases of its development, but the early results do seem to suggest that it’s worth pursuing. And to bring this back to an idea we mentioned earlier, for a treatment to be effective on a large scale, it has to be accessible, and TMS does have the potential to be incredibly easy to access.

Jacinta O’Shea: In terms of other future developments, and this is something that Covid has sort of helped to boost as well, trying to miniaturize the ways of delivering these stimulations so that people can take them home and self-administer them. This is a bit more challenging to do with TMS, although people are working on it, but there are related forms of non-invasive brain stimulation that you can place on your head, sort of like those headphones you’re wearing, and it non-invasively delivers stimulation.

I should say that this is not yet an approved treatment. So this is very much in the domain of experimental investigation, although there are people who on the internet build their own versions of these things — not to be advised — but there is some evidence that you can get antidepressant-like effects from these other forms of stimulation. What’s attractive about that is that they’re relatively cheap, they’re mobile, that people could take them home so they wouldn’t have to come into hospital every day with all the infrastructure that’s required around that.
**Dan Merino:** I want to come back to Joe Finn’s point about humility here because it really does apply to this moment in neuroscience. TMS and DBS — yes, they are fantastic, but there’s still so much researchers don’t know that there’s no reason to assume we can’t do much better.

**Joseph Finns:** Lewis Thomas, who was the famous physician who wrote *Lives of a Cell* and won the Lasker Prize and the National Book Award, he had this phrase about halfway technologies, right? That we, you know, we have halfway technology. So the iron lung was a halfway technology to the ventilator, to the polio vaccine, which was the final step in that sequence. Each thing helped, but they were halfway technologies, and I think we have a lot of halfway technologies right now in neurology.

**Gemma Ware:** I think this is so important, to see both where we’ve come from and where we’ve gone to place ourselves in history, and then imagine also what’s gonna happen a hundred years from now, because people might look back on these treatments and say, well, that was way before we had the cure for “X” that we have now.

**Dan Merino:** Right? And even knowing that we’re only halfway to somewhere, and that there’s still so much to be done, it’s important to appreciate how much progress has been made, yeah, because science is cool, but also because it’s helping real people. And I want to give Moksha the last word.

**Moksha Patel:** At least for me, it has not been a cure. And I think for most patients, it is not a cure. I went from severe or extreme OCD to moderate OCD. But it went from feeling like I was completely on prison to maybe being on house arrest, you know, where I have a little bit of, some restrictions, but I’m back in my home. I have, you know, um, I. I just have hope again, you know, it really feels like that.

**Dan Merino:** That is it for this week. Thank you so much to our colleague, Amanda Mascarelli in the US who worked with Rachel Davis to tell her story on The Conversation. We’ll put a link to that in the show notes for this episode.

**Gemma Ware:** You can find us on Twitter: @TC_audio; on Instagram: @theconversationdotcom or email us: podcast@theconversation.com If you like what we do, please support our podcast and the conversation more broadly by going to donate.theconversation.com

**Dan Merino:** This episode of The Conversation Weekly was produced by Mend Mariwany and Katie Flood. It was written by Katie Flood and me, Dan Merino. Sound design was by Eloise Stevens and our theme music by Neeta Sarl. Stephen Khan is The Conversation’s global executive editor. Alice Mason runs our social media, and Soraya Nandy does our transcripts.
Gemma Ware: And I’m Gemma Ware, the show’s executive producer. Thanks for listening.