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# The Network Effect: Analyzing Brain Structures to Treat Depression

**ReachMD Announcer:**
Welcome to Advances in Care on ReachMD. This medical industry feature is titled “The Network Effect: Analyzing Brain Structures to Treat Depression.” These podcasts are a production of NewYork-Presbyterian with doctors from Columbia & Weill Cornell Medicine.

Here are your guests, psychiatrist Dr. Conor Liston and health and science journalist, Catherine Price.

**Catherine Price:**
Dr. Conor Liston didn't set out to study Transcranial Magnetic Stimulation, a practice in which doctors aim powerful magnets at the brain. But that changed when he began mapping the brains of people with depression. He and his team saw that people suffering from major depression had physical differences in their brains compared to those who were not depressed. Some sections of their brains had expanded and pushed into others. And something clicked for Dr. Liston. If the maps he had created showed how depression was changing depressed people’s brains, then maybe he could use Transcranial Magnetic Stimulation, or TMS for short, to treat just those changed areas.

I'm Catherine Price and this is Advances in Care.

I recently sat down with Dr. Liston, attending Psychiatrist at NewYork-Presbyterian / Weill Cornell Medicine, to talk about his research on brain mapping major depression and how understanding depressed brain structures could lead to revolutionary treatments.

Thanks so much for making the time to talk to me today.

**Dr. Connor Liston:**
Well, thanks for having me. I'm really excited to be here.

**Catherine Price:**
So, tell me a bit about what depression actually is and what interested you in studying it.

**Dr. Connor Liston:**
Yeah, absolutely. So, major depressive disorder is a name for a syndrome. Which is a group of symptoms that tend to co-occur in many individuals. And we diagnose depression today when a patient presents with five or more of this list of nine symptoms that include things like low mood, anhedonia, a loss of pleasure in activities the person used to enjoy, changes in sleep, appetite, weight, physical activity, other symptoms as well. And doing some quick math, if you can meet these criteria by having five or more of nine symptoms, that means there are at least 256 unique combinations of symptoms that you can present to your doctor with and still get this diagnosis and that's not even accounting for the fact that many of the criteria contain opposites of themselves, like sleeping too little or sleeping too much, a loss of appetite or, an overactive appetite, eating too much food.

**Catherine Price:**
I mean it's really surprising that those opposite symptoms can occur in people with the same condition. That’s just so strange.

**Dr. Connor Liston:**
It is strange. I remember having this experience as a medical student, learning about it and kind of being puzzled by it, and it's actually one of the things that really drew me to the field. Are there ways that we could do this better?

**Catherine Price:**

Gotcha. So, before we get into how you're making it better, can you tell us what treatment currently looks like for people with depression and also what happens when patients have cases of treatment-resistant depression?

**Dr. Connor Liston:**
So, if you, say you're a young person, like in your early twenties, and you get depressed for the first time, what's likely to happen is, a diagnostic workup, a confirmation that this is in fact major depressive disorder and then a discussion of treatment options, and, as a first line treatment, the most commonly used options are either a medication, a selective serotonin reuptake inhibitor, like Prozac, or psychotherapy, which is probably just as effective as a medication in mild to moderate cases of depression, meaning a structured evidence based psychotherapy, like, cognitive behavioral therapy.

And, hopefully one of those two things will work for you. But, the odds are, at least as likely as not, that you won't achieve full remission from your depression, during a trial of one of those treatments. But if you're in that group of people, and it's not a small group of people, for whom neither of those first two steps was effective, then there are a whole host of other options that are more complicated, but that have been shown to be effective for treatment resistant cases of depression, and one of them is ketamine. A particular version of ketamine, S ketamine, just got FDA approval, for depression, so that's one option that can achieve prettyrapid antidepressant responses in some people, and another option is transcranial magnetic stimulation. That's one we're very interested in here at Cornell and NYP. Transcranial Magnetic Stimulation, or TMS, is an office-based treatment that stimulates the brain, using magnets, effectively.

So if you were a patient, you'd come into an office, you'd sit in a big kind of lounge chair that's specially designed for this purpose, and a high powered magnet that's the size of my forearm, approximately, would be positioned over a particular location on your scalp and the magnet has been programmed to deliver high frequency, highly potent magnetic field pulses, which cross the scalp and generate an electric field inside the brain and that electric field generates currents and activates brain cells. It uses high-powered magnetic fields to stimulate the brain, and with repeated stimulation, we think that, that engages kind of plasticity mechanisms in the brain, it changes the way brain cells are connected to one another, and many patients who have not responded to other kinds of treatments, do get better, in response to TMS.

**Catherine Price:**
I mean that’s incredible, so can you tell me a bit more about what makes TMS a good candidate for treating depression?

**Dr. Connor Liston:**
We're very interested in TMS for several reasons. One is, it's a treatment that has a lot of different parameters that you can adjust and adjust there's, I think, a consensus that there's probably better ways of delivering TMS than the way that we currently do. And so, it seems like an area where my team could have an impact on improving patient care if we could just figure out how to deliver it more effectively.

Another kind of scientifically appealing aspect of this treatment is that it is relatively focal. And by focal, I mean, that drugs like Prozac, you ingest them orally. They go all over your body, they bathe your brain, and they probably have effects all over the place. And, in contrast, TMS its direct effects are really limited to the area that you're pointing the stimulator at. So, there's more controllability to it. And then a third feature of TMS is that it's rapid, relatively so, whereas with Prozac, typically four to six weeks of daily treatment is what's required to know whether it was effective or not.

With new forms of TMS where you can, condense six weeks of treatment into a single day. A person comes into your office, they get there, eight or nine in the morning, and they stay until six or seven at night, and they get treatment on the hour every hour, and they get six weeks’ worth of treatment in a single day, and then you can repeat that Monday through Friday, and many of those patients show really potent, rapid responses to TMS. And so that's great for patients, and it's great for doctors. So that’s really appealing.

**Catherine Price:**
It's truly remarkable that patients can improve so quickly with the treatment.

**Dr. Connor Liston:**
It is really remarkable, I came to TMS from outside the TMS field, we didn't, in my lab, start as TMS researchers, and so, like anyone else, when I first got into it, I wasn't exactly sure what to expect, how what I had read in the literature would comport with my personal experience of helping people and interacting with them.

And when it works, it really is really quite remarkable. There are some individuals who have been suffering from OCD in a kind of unremitting way with really severe disability and they come in on Monday and they get the treatment and sometimes it's very difficult for them to even make it to the clinic, because of their OCD symptoms. But they figure out how to do it, and they come in and they get their treatment and then, they come back the next day. And at the end of the next day they seem like different people sometimes. And they'll

tell you that there was a time when I couldn't leave my house, and today I rode the bus to come see you at the clinic just to test it out, and, I wasn't free of symptoms, but it didn't bother me so much, and here I am, and it's really quite remarkable when it works.

**Catherine Price:**
I mean that's just astonishing. What do you think is happening in the brains of these patients being treated with TMS?

**Dr. Connor Liston:**
With TMS, there are many different parameters like where you're pointing the stimulator, what orientation the stimulator is positioned at what frequency the pulses are delivered at, how strong the pulses are, how many sessions they get, how many sessions per day, the time in between the sessions. All of these things probably matter a great deal and so one of the things we've been doing in the lab is trying to model these features in mice, in animal models, using optogenetic tools, which allows to mimic what TMS is doing, but with much more experimental control.And what we found is consistent with I think a consensus in the field, there's probably multiple mechanisms involved. One of them involves plasticity, in neurons, at the target site for TMS, so like right where you're pointing the coil, meaning that connections between those neurons become strengthened in response to repeated stimulation.

But then there are probably also other mechanisms that involve kind of network effects, where when you stimulate this brain region. Other brain regions that it's connected to will also be indirectly stimulated and using mouse models, we can control that with much more precision. We can ask, we can create maps, for example, throughout the brain, which brain regions are activated by this kind of stimulation, which brain cells within those regions are more or less activated.

And then if we go in and silence one of those brain regions while delivering the stimulation, does that disrupt the antidepressant effect? And we think that it does. We're still working that out. But, that's where the field has converged at this point that, there are local effects that involve strengthening connections between cells, but also probably network effects that are responsible for, dissociable kind of components of the antidepressant response, appetite, sleep, hedonic function, mood, etc.

**Catherine Price:**
I'm wondering if you can talk a bit more about the work you've done about how our brain structures actually affect the presentation of depression and the treatment. Because I understand that you've done work showing that we're not all the same when it comes to this.

**Dr. Connor Liston:**
Absolutely. That's a big area of interest for us too, and it's especially relevant for TMS, it being a brain stimulation treatment that relies on these brain networks. So for years now, we've known that the brain is organized into functional networks, that have names and that exist in approximately the same place in all of our brains.

And you can think of these networks sort of like our airport network, where you have airports that are connected to one another to varying degrees, and if you are located in a hub city, like New York or L. A. or Chicago, it's probably very easy for you to get to a whole host of other cities without making a stop, but if you're in kind of Portland, Maine, or a smaller community, and you want to get to Portland, Oregon, chances are you're going to have to connect through at least one of those hubs.

So, we think the brain is organized in a similar way, into this kind of hub-like Network structure, and this is one reason why dysfunction in hubs in the brain can percolate out into the rest of the brain and lead to all sorts of unexpected effects. So, it turns out that those networks that I just described are located, and you know approximately the same positions in all of our brains, but recent work from a number of groups at Stanford, Harvard, Wash U, here at Cornell, other institutions as well has shown that there are important individual differences in the precise boundaries of those networks.

**Catherine Price:**
So how did you come to figure out about the differences in those boundaries?

**Dr. Connor Liston:**
Yeah. So, we obtained fMRI brain scans from all of the patients going through our clinical trials, and also from a smaller set of people who were generous enough to volunteer their time. to come visit us repeatedly as they cycled in and out of depressive episodes. And in these individuals, we have very precise maps of exactly what their network boundaries look like. And just like a map of the United States, the map in your brain doesn't really change. It's very stable over time. And it turns out that people with depression in this sample have a particular network, the salience network that is massively expanded.

**Catherine Price:**
Oh, that's really interesting because in a lot of my external work, I do things related to focus and attention. So, I actually think a lot about the salience network, which is, as a reminder to people is the part of the brain that helps us detect what stimuli is and is not important. So, we can choose what to pay attention to. So how big was it in relation to non-depressed brains?

**Dr. Connor Liston:**
So approximately twice as big.

**Catherine Price:**
Wow, okay

**Dr. Connor Liston:**
Which is massive for these kinds of measures, in some people it can be up to four times as big, but approximately twice as big on average. It's a very big effect. You don't need any fancy statistics to see this. You can just look at a depressed brain and look at a not depressed brain, and you don't need any special training to see that, like, this one is twice as big as this one. It's very obvious. Yeah, it's very obvious.

**Catherine Price:**
That is absolutely fascinating. But does that, so does that expansion change depending on whether you're depressed or not depressed? Like could it become then smaller over time and then bigger again? How does that work?

**Dr. Connor Liston:**
You know, there's many questions that we don't know the answers to yet, but we're working on. Like, we don't know, the mechanisms that give rise to this expansion, or how early it emerges, whether it's a product of being depressed, or a cause of getting depressed in the first place that kind of precedes the onset of your depression, but one hint of that, came from a pair of studies. This by the way is work by, Chuck Lynch, an assistant professor in our group
He scanned, as I said, a group of people, a small number of people, dozens of times over a course of a couple of years.

And our hypothesis was that this network expansion, that we might see it, like, grow and contract as a person became depressed and not depressed. And what we instead found was very clear evidence that our hypothesis was wrong. The expansion that was detectable in these depressed people was very stable.

It didn't change when they got better. It was always there. And that led us to ask whether it might be the case that instead of driving the emergence of this mood state, depression, maybe it's a marker of risk for becoming depressed in response to triggers like stressful life events.

So, we kind of like puzzled over how we would go about testing that. and it's a challenging thing to test. I ideally like to be able to track people before they ever get depressed and follow them over time, and that's hard to do. But we did find one solution to that. We teamed up with a consortium of investigators.

This is a project called ABCD, Adolescent Brain and Cognitive Development kind of program, which has been tracking thousands of youngsters a community sample, mostly healthy kids, but some people with psychiatric conditions, just by chance. and we were, out of those thousands of people, we were able to identify a few dozen, I want to say about 60, who were scanned at ages 10 and 13, never depressed at that time, and then went on to become depressed at age 13, in adolescence. We were able to ask whether their salience network was expanded before they ever got depressed and we found that it was.

So, we think that this kind of expansion emerges early in life and might confer risk for later becoming depressed.

**Catherine Price:**
I have this question for everything you're telling me, but what might the implications be for future treatments if that were to be the case?

**Dr. Connor Liston:**
Yeah, so it's fun to speculate, like there's a lot of work that would have to, that would have to be done, before we'd envision any of these kind of implications becoming a reality.

You could imagine that kind of marker being useful information for patients, for doctors, for family members, where a scan might be useful in some individuals. We're not envisioning, that it's ever going to be the case that, hundreds of millions of people are going to need to get MRI scans, but you can imagine some individuals where having this piece of information can tell you a little bit about what your risk is, for getting depressed in response to triggers, and if you are at elevated risk, just like all sort of other markers we use for stratifying risk in medicine, blood pressure, blood glucose, BMI, et cetera, knowing this information might be useful to start healthy interventions that are easy to integrate into one's life that might be useful for mitigating risk, that's one possibility.

I think a second is, knowing that this network is so expanded in depression, probably has implications for how you deliver brain stimulation treatments like TMS. But I think the field is converging around the idea that these brain networks may be important for understanding how the brain responds to treatments like TMS, and they might be important for predicting why some people get better in

response to TMS and why others don't. And you can imagine that if you've got this network that's two to three times as big as it in one person as it is in a lot of other people that stimulating in those individuals with, in which is expanded, might lead to very different effects.

And so we're trying to, collect data to model that and to understand it better. And I think it's going to take a little time, but I think it's likely that it will be useful to incorporate into our protocols for how we think about targeting TMS.

**Catherine Price:**
So, I'm curious what that would look like in practice …like how might it affect actual patients receiving TMS?

**Dr. Connor Liston:**
I'll give you one example. So, you can imagine how if the salience network is expanding some other networks must be shrinking. because there's a fixed amount of space in your brain. And what we found is that that is true. Other networks are shrinking. and it's largely due to encroachment of the salience network onto neighboring networks.

And interestingly, it doesn't work the same in all people, so we were able to identify three different modes of encroachment, where in one group of people, for example, the salience network might be expanded at the expense of this other neighboring network, we'll call it A, it doesn't really matter, and in another group of people, A is not at all contracted.Instead, the salience network has encroached onto network B, and in a third group of people, it's kind of a combination of B and C, for example.

And, we think that the way that these networks are shrinking in conjunction with the expansion of the salience network might have implications for different kinds of cognitive functions and your ability to respond well to different kinds of treatments.

We know that some of these networks that are shrinking are important in, a set of functions we call cognitive control, which basically refers to your ability to control your cognitive resources, attention, memory, other functions to adaptively adjust how you're allocating those resources to achieve your goals. And we think cognitive control is very important for, Cognitive Behavioral Therapy for engaging in therapy, for example, also for other kinds of therapy, for obsessive compulsive disorder.

And so, you can imagine this is years off, but you can imagine formulating predictions about how. The kind of contraction of one network might lead to deficits in the ability to engage certain kinds of cognitive functions and benefit from a particular kind of treatment. And perhaps those folks would do better with a different kind of treatment. And that's something that we're working to test.

**Catherine Price:**
Gotcha. So, in other words, like, if you were having trouble sleeping, it could be because the part of your brain that controls sleep is actually being affected by a different part of the brain. So, it sounds like what you're working on is figuring out how to customize treatment based on what specific parts of the brain are causing the symptoms, right?

**Dr. Connor Liston:**
That's right. That's one of the goals. So, we've been interested for a while now in using fMRI brain scans and those kind of connectivity maps to try to discover subtypes of depression. We use a particular kind of fMRI scan called a resting state fMRI scan. This particular kind of MRI scan has been sensitized to to neuronal activity, indirectly. It's actually measuring the level of oxygenation in the blood.

If you have a particular brain region that's becoming more active, the brain detects that and responds to it by delivering more blood to the area, resulting in a change in the amount of blood that's in that area. If two regions are connected to one another, then when one becomes active, the other is going to tend to also become active because they're connected. And so, you can measure how correlated those brain signals are, over time, as a kind of indirect measure of how connected they are. And that's the basic idea.

**Catherine Price:**
Is that like mapping out your, the airport network to see how many connections there are between Philadelphia and Atlanta?

**Dr. Connor Liston:**
Exactly. You can think about it as, like, how many planes are flying between JFK and Chicago O'Hare on a given day.

**Catherine Price:**
And how did you actually analyze this data? Can you talk a bit about the role of machine learning in this?

**Dr. Connor Liston:**
So we think that machine learning, we and many folks in the field think that machine learning is going to be really valuable in advancing our understanding of depression biology, and rethinking how we do things, based essentially on the premise that we don't know that much, not nearly as much, as we would like about depression biology at the moment.

And so, the idea with machine learning is, let's not impose our, like biases or, preconceptions about what's going on in depression,

based on the assumption that maybe there's a lot that we don't know, and let's let the data tell us what's happening and follow where the data leads us.

When we get those brain scans, we can measure the strength of connections, between hundreds of different brain regions, and that gives us this map that is, like 30, 40, 50, thousand different connections, many of which probably have nothing to do with depression, but some do, we kind of operate under the assumption that we have a pretty good idea about some of them, but there's probably many that we don't know yet. You can train a computer to differentiate depressed brains from not depressed brains based on these connections.

And that lets the computer kind of tell us which ones are the most important. Instead of honing in just on the strength of connections between LaGuardia and O'Hare, let's look at connections between each airport and every other airport in the country and maybe in the world and let's, see which connections are most important.

**Catherine Price:**
The problem's in Topeka and you just never realized.

**Dr. Connor Liston:**
Exactly. And I think we and many others in the field are finding that's true. Like, for example, the primary motor cortex. This is a strip of your brain that's right here, on the side and it's the area that kind of initiates movements of any kind. And it's not necessarily the first area you would think about when you think of depression. What does motor activity have to do with depression? And it's not an area that people have typically studied in depression, but many of our studies and other group studies as well are beginning to implicate changes in motor cortex in depression. And now that we know that, you can imagine, ways in which motor cortex might be very important. We do see that in many patients where often the thing that they're complaining about most is like, I don't have the energy to get out of bed. Like I'm immobile.

**Catherine Price:**
Well, that's interesting. Like, I don't think I've ever, I've never been actually depressed, but the closest time I come to that, I do remember, it was like I could barely pick my feet up.

And I remember, slumping down the kitchen wall and then sitting on the floor and thinking, this looks very dramatic. Do I really need to be doing this? But I felt like I didn't have control over it. It was just something that was happening.

**Dr. Connor Liston:**
Exactly. And I think, like, not everyone gets depressed, but everyone encounters, grief at some point in their life, and grief and depression have some similarities, and a lot of people with severe grief have that same experience of really embodied locomotor aspect to their grief or to their depression.

**Catherine Price:**
It must be really validating to both to you and I would think to some of your research subjects where, you know, there's you worry that some of this is quote just in your head. Which it is. But you're discovering why it's in your head. It's like ‘oh just get over it,’ you know, get out of bed. And it's like well, ‘no actually we're figuring out what's going on in your brain.’

**Dr. Connor Liston:**
That is a hundred percent true. I can think of a half dozen patients I've interacted with just off the cuff who've had that experience and being able to show them something like that expanded salience network I think would be really empowering and therapeutic in many ways. There's this suspicion that right that what they're suffering from is just a character traits, a kind of defective response to a lot of stress in your life, and seeing that there's this kind of biological phenomenon that you can visualize with the naked eye I think could be really powerful for some people for de-stigmatizing depression.

**Catherine Price:**
Well, thank you so much for making the time to talk with me today.

**Dr. Connor Liston:**
Thank you. It was really fun. I'm glad we were able to do this and thanks for making time for it.

**Catherine Price:**
Huge thanks to Dr. Conor Liston for taking the time to talk to me about his research into the diagnosis and treatment of major depressive disorders.

I'm Catherine Price.

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