Nicole Rust on her new book, 'Elusive Cures'

Rust discusses how understanding the brain as a complex dynamical system will help us accelerate treatments for brain disorders.

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

Nicole Rust
He said, "I spent 13 years heading this agency. I spent $20 billion, we did all this cool neuroscience, and we did not move the needle on helping individuals that have mental disorders." That was a wake-up call for me, and there are all sorts of calls like that. I now like the idea of fast-forwarding to the end and ask, what does society need from us? Then go backward and fill in those blanks. One of the biggest unanswered questions is the neuroscience of feelings. The most profound insight, I think, that follows from thinking about the brain in this new way is how hard the end goal of treatments really is, because we know that complex dynamical systems are exceedingly hard to control.

[music]

Paul Middlebrooks
This is "Brain Inspired," powered by *The Transmitter*. *Elusive Cures: Why Neuroscience Hasn't Solved Brain Disorders—and How We Can Change That*. She is Nicole Rust. You've heard her or seen her before on this podcast. I am Paul. Nicole runs the Visual Memory Laboratory at UPenn, University of Pennsylvania. Her interests have expanded now to include mood and feelings, as you'll hear. She wrote this book, which contains a plethora of ideas about how we can pave a way forward in neuroscience to help treat mental and brain disorders.

We talk about a small plethora of those ideas from her book, which also contains the story partially, which you'll hear of her own journey in thinking about these things from working early on in visual neuroscience to where she is now. There is a tinier, tinier plethora of show notes at braininspired.co/podcast/214, where there's a link to the book as well. Here's my discussion with Nicole Rust.

[transition]

First of all, Nicole, last time your voice was heard on this podcast was a few years ago, and you were talking about lumens and the importance in your life of getting enough lumens for your mood.

Nicole Rust
That's right.

Paul Middlebrooks
I know that your interest has transformed from memories to mood. Now I'm putting the pieces together, and I thought, "Maybe mood already was a thing that you were interested in back then, so you wanted to make sure that you got enough lumens to keep a healthy and happy mindset." I see that there are a few lumens coming through a window behind you. My first question is, are you getting enough lumens these days?

Nicole Rust
[laughs] Yes, I have both a south-facing house and a south-facing office. I get lots and lots of lumens. Yes, no, thanks for bringing up that memory. I totally forgot about that. Yes, it's true.

Paul Middlebrooks
That might come back into play in our conversation on how to understand brains and treat disorders. You're here to talk about your new book. Is it backwards to you? *Elusive Cures*?

Nicole Rust
No, it looks forwards to me. Yes, absolutely.

Paul Middlebrooks
Elusive Cures: Why Neuroscience Hasn't Solved Brain Disorders—and How We Can Change That. Just a moment, right before I hit record, we were talking about how books take a lot of work, a lot of research, take a lot of time. Then, like a paper, when they finally come out-- and this will have been out for a couple days once this is released, so I'll link to it so people can go buy it. Once it comes out, it's almost in the past already because you've moved on in some sense, like a research paper.

We were talking about just the massive amount of work that went into it, all the different disparate kinds of examples that you use and stuff, and of course, we're not going to go through everything. One thing I like about this book is that-- We'll talk about the central themes here, and then we can get in the weeds if we want to. One thing I like is that you document your journey in thinking and understanding what brains are, how they function, et cetera.

I have not been on as long of a journey as you, but I see my own reflection in this journey, so it was exciting to me to see someone with that same sort of spirit. Recently, I started this complexity discussion group where the SFI, the Santa Fe Institute, just released this giant four-volume collection of foundational papers in complexity, and the goal of this group is to go through every damn paper, and because I want to assimilate it into my own thinking, and have it affect my own research.

Nicole Rust
It's wonderful.

Paul Middlebrooks
We've had a few. They've been very fun. The reason I'm bringing this up is because the last one that we did was McCulloch and Pitts, 1943, with the first artificial neurons. I thought, "Everyone already knows about this will be an easy one to go through." Turns out the math is hard in it. Aside from that, after the discussion, I went into lab and I was telling someone what just happened. We went through McCulloch and Pitts. This was a first-year graduate student, and this person was like, "What's that? I don't know what that is," and I was like, "What?"

Nicole Rust
Oh, you have to know.

Paul Middlebrooks
That's what I said. It's like, "Oh, you need to know this," but I didn't know that when I was a first-year grad student. I was so naive, and there's so many things I didn't know. I'm still learning.

Nicole Rust
We all are.

Paul Middlebrooks
We all are. Like I said, one of the things that I like about this is I get to sort of live your own personal journey here. I wanted to start by maybe you just reflecting on where you came from and how you got to where you are now.

Nicole Rust
Yes, absolutely. Thank you for all that. Yes, I feel like in some ways you and I have been on this parallel journey of zoom out and think about the big picture as we also in parallel dive in into the nitty gritty and do research.

Paul Middlebrooks
One big difference is you have tenure. That's a big difference.

Nicole Rust
I do have this wonderfully privileged position, yes, which is great. How did I get here? For me, it all started when I was an undergrad. I grew up in small town USA in North Idaho in the little, the skinny part of Idaho, the panhandle up there near Canada. I went to the University of Idaho as an undergrad thinking I would be an engineer. My father was an engineer. My uncles were engineers. My grandfather was an engineer. I thought this is a great job. I'm going to be an engineer. I didn't find my first year coursework to be really inspiring, let's say.

I was looking for something else to spend my life doing, and that's where I encountered Francis Crick's book. Francis Crick, as we all know, in the first part of his career, he helped elucidate the three-dimensional structure of DNA. Then later in his career, he became a neuroscientist, and he wrote this book in the early '90s called *The Astonishing Hypothesis: The Scientific Search for the Soul*. I just woke up to the idea this could be a job. Scientific searching for a soul could be a job. I was absolutely hooked at that point.

Crick planted the seed in that book that a route into the big mysteries of the brain. He was really interested in consciousness and free will, but he said the route in is in the visual system, because the visual system is a very tractable system in terms of-- it's very intuitive to us because we are such visual creatures, and so if we understand the visual system, that will be the key to unlocking some of the big mysteries. Yes, I carried that with me. I don't know that it was really explicit. When I look back on it, I think I forgot about that book. I became a neuroscientist, but then I went and studied the visual system for many years. And for me-

Paul Middlebrooks
Part of that book also, this is the height of the molecular biology world. I think, didn't you get a major in molecular biology?

Nicole Rust
I did. I have a major in molecular biology. Absolutely.

Paul Middlebrooks
I think that's my major also.

Nicole Rust
Yes. That was a really nice nexus there between biology, but also a little physics-inspired and chemistry-inspired math. Yes, absolutely. At the time, there was this idea that the seed of consciousness might be some special set of neurons that express some special protein. That was one of the theories on the table. That book, yes, really captures the old way of thinking about how the brain works. From there, I studied the visual system, but the idea for me was always we just want to use what we've learned and then go bigger, and so I marched bigger and bigger throughout my career.

Bigger being deeper, I would say, cognition. I moved from studying early stages of the visual system, how does the brain figure out what direction something is moving, to bigger questions like how do we recognize the objects we're looking at, and then how do we find the objects we're looking for, how do we remember what we've seen? Then following on the insights from this book, I'm now redirecting my research program to study even a bigger mystery, and that is mood, so what in your brain drives your experience of happiness, and how does your brain shape that experience?

Paul Middlebrooks
First of all, let me say, it's interesting to me. Going back to the Crick influence, that's a very reductionistic approach, like you said, that the old way of thinking, which is still very much the modern way, in mainstream neuroscience, maybe, I think, not in my world.

Nicole Rust
I think that's changing. I definitely think that's changing. That's a thesis of my book.

Paul Middlebrooks
Yes. You're helping it.

Nicole Rust
That's changing. Yes.

Paul Middlebrooks
You're helping it change, also. Then, some of your early work on visual cognition, thinking about untangling representations, which is like the manifold, idea, which is already getting away from-- It's toward the dynamical systems view, away from that single neuron view. You already had a head start early in your career, but I'm wondering, did you have your modern view where the seeds-- How did your modern view grow over time? Was it planted in that early work, which looks very much like it would give rise to your current way of thinking?

Nicole Rust
That's an interesting question. I definitely was part of that industry of thinking about the brain is an information processing machine. It takes information through its senses and it transforms it as it propagates through the brain to support behavior. I would say, especially that move to thinking about how our brains recognize objects and thinking about populations of neurons, that was such an important moment for me. I did my postdoc with Jim DiCarlo at MIT.

The most exciting part of that for me was the idea that we didn't have to systematically march to the brain, one brain area at a time, because I thought that was the agenda we were on. We figured out V1. Then we had to figure out V2. Then once we figured out V2, we could go to V4. Once we got to V4, we could go to IT. This new way of thinking about the brain was, "We don't really have to understand how IT came to be. We just have to understand what it is. If we understand that, we can leapfrog over all of that stuff that we don't understand. Then we could push things even further."

That notion of trying to figure out how representations are changing by leveraging what they are and what they're changing to, I think, has been a really important one for me and for the entire field. It's exploded so much and enabled so much in the realm of internal representations and cognition. I would say that I was very dubious about the whole dynamical systems thing until I wrote this book. I'm surrounded by people who study things like this.

I had some experience with it early in my career, and it just seemed to me to be really important for things where the brain might be oscillating, like walking or breathing. It also seemed to me-- I just didn't get why it was important or useful, until I wrote the book. Then I zoomed out and I realized, "Oh, wow, there's something missing here. If we're just going to explain the brain as a big feed forward chain, we've missed one of the big punchlines." That was hugely insightful to me.

Paul Middlebrooks
Yes. As I was talking, I realized, I guess you can still, if you're studying something like inferior temporal cortex, IT, and object recognition, you can still think of the brain as what you call in the book, a domino-like information processing system. Even within a dynamical systems perspective, you can think of it as this feed-forward propagation thing. If you're just studying the thing that's changing, you don't need to worry about all the massive recurrence, which you write about in the book as well.

Nicole Rust
Yes.

Paul Middlebrooks
All right. Then you studied visual memory and now, like you mentioned, you've switched your focus pivoted, I suppose, a little bit to studying mood. Then I thought, oh, which preceded? Did your interest in mood lead you to write the book, lead you to realize that there was missing things in the from bench to bedside treatment paradigm that's supposed to happen, that I heard a lot as a graduate student. I was like, "This is not how my work goes." Did the interest in mood precede that, or did the process of writing it also bring that up about?

Nicole Rust
Yes, that's a great question. First of all, who isn't interested in mood? It's just this fascinating, mysterious thing. The word that word drives all of us and it drives our motivations, like who isn't curious about it? There are a lot of things I'm curious about in terms of how the brain works, and mood is among them. Consciousness would be just like another one. Just the phenomenon of consciousness is I think also fascinating. Why mood on the other side? I think part of it-- I also early in my career, it was very driven by just curiosity.

I just want to figure out how the brain works. I am in pursuit of the scientific search for the soul. I want to figure out how we work. I always also bought into the idea that my curiosity was a win-win for society. Like just what you said, that's the bench to bedside. Brain research is shaped around this premise that the bottleneck to an impactful understanding of the brain is just understanding the nuts and bolts of its healthy function. I always like to use the analogy of we would never expect a mechanic to fix a car without understanding a car.

We train them, we give them a manual, it describes how the car works, but our physicians are dealing with manuals and they're just full of these blank pages. How can we expect them to be effective? We, as foundational basic researchers, are in charge of filling those blank pages with information about how the healthy nuts and bolts of the brain work. When I encountered-- it's a long time, I just bought into like, "This is working."

Then I started to hear murmurings from the highest stages. The heads of the National Institute of Mental Health, Thomas Insel, when he stepped down from his position, he said, "This isn't working." He said, "I spent 13 years heading this agency, I spent $20 billion, we did all this cool neuroscience and we did not move the needle on helping individuals that have mental disorders." That was a wake-up call for me and they're all sorts of calls like that.

Paul Middlebrooks
You could have taken that message and still said like, "Yes, but this research that seems in the abstract, it does lead to progress and understanding." Then maybe it's just farther down the road that those pages will get filled in and I can just continue on where I'm going. There's something inside of you that said, "No, I need to address this," right?

Nicole Rust
Yes, because I felt like I couldn't answer that with a straight face. I just didn't know enough about. As researchers, I were deep into our thing and at that point I was studying visual memory. I knew a lot about visual memory, and what I thought that particular research would be good for. I felt like I didn't, have really good responses to, say, Tom Insel at the National Institutes of Mental Health. I was really just interested, and I realized like, "I don't even know how brain research actually works at a high level."

There is the sense that it's supposed to work by bench to bedside, but you also hear there's so many of our drugs that were discovered serendipitously before we understood the brain. I just really wanted to dive in and really understand it. The other thing that's driving me too is I felt like-- we have lots of criticisms about the reductionist approach, but I couldn't really spell out like what is the genius of our era? When we fast forward in 30 years and we look back and we say, "What was the big game-changing thing that we did to unlock all the wonderful things?"

I couldn't spell that out in a coherent way that I felt really confident about. That's really what motivated me to write the book. Writing the book, it was a big zoom out for me. I studied all sorts of functions and dysfunctions, motor control and paralysis, mood and depression, everything, stroke, sanity and psychosis. On the other side of it, I had the great privilege to ask myself, "Okay, things have changed for me. Up to this point, I've treated the brain as a domino chain. I'm embracing the idea that that's not the type of thing that the brain is, or that's not a good description of what we need to know about the brain. Now, where do I want to dive back in?"

The thing that excited me the most, due to this confluence of, I do think about it differently now. I think that I'm still a foundational researcher. I'm still a basic researcher, hands down, no question. I now like the idea of fast-forwarding to the end and ask, what does society need from us? Then go backward and fill in those blanks. One of the biggest unanswered questions is the neuroscience of feelings. Just all the other functions are progressing at such a faster clip.

If I show you a picture and I ask you what's in it, if I ask you, 'Have you seen it before?" If I take this bottle and I ask you, "Can you reach out and grab it?" We're just like making such fast progress and understanding how the brain does all those things. If I ask you, "Hey Paul, how happy are you right now?" We know very little about what in your brain is driving your experience and your response. We know very little about how your brain shapes that experience.

There are good reasons for it. There are bottlenecks there. Mood is harder than other brain functions. It's not that the depression researchers have been sitting on their hands. It was the unmet need there that made me want to dive in and contribute to filling that hole. It's still very much from the perspective of just a nuts and bolts understanding of how mood fluctuates in a healthy everyday brain, not clinically.

Paul Middlebrooks
You said clinically, and that's what I was going to ask. Is part of the challenge with something like mood that we don't have a great-- With object recognition, we can measure it very easily. With mood, I don't know where the psychological basis descriptors of mood are, but is it something that we don't understand enough at a descriptive psychological level to start measuring the right things in the brain?

Nicole Rust
I would say that the central bottleneck does-- it is what you're hinting at, but it's a little bit different, and that is for all the other brain functions I mentioned, so seeing, memory, motor control, you can actually shape a task and use objective ground truth as a benchmark. I can give you a memory test and there will be a right answer to the question. There is no right answer to the question, how happy are you?

Nobody knows how happy you are, but you, and there's no happiness you should be arguably. That means it's really a subjective experience for which there's no ground truth. That in turn means it's very difficult to measure in animals. In animals, we have hands down our best measures of neural responses at the resolution we need to figure out how the brain works. We also do all these amazing manipulations now in this era with optogenetics.

It's really hard to study the neuroscience of feelings in animals. That's the bottleneck that we really have to get through in order to, I think, create a neuroscience of mood is wrapping our heads around, what do you do when you're trying to study a subjective experience? You have to approach it in a different way than you study these other brain functions.

Paul Middlebrooks
I did just come from a conference at Georgia Tech. It was InterfaceNeuro. It was all about brain computer interfaces and the modern technology driving stimulation of brain in humans, modulating brain activity and these closed-loop feedback kinds of circuits. They even had patients who had been treated with these technologies in the audience asking questions. Also, there was a separate storytelling where they evening where they told their stories.

I came away surprised, because you know all this cool stuff's going on. Then to see it all together, the tone was super optimistic at this conference, which is different than a normal conference or whatever. I came away from that fairly optimistic myself in terms of using humans as our model animal. Maybe something like mood, maybe this brain computer interface population would be useful for that, no?

Nicole Rust
No, I think human neuroscience is unquestionably going to be part of the solution for mood research going forward. There's also you're always up against these restrictions. You can't do optogenetics in humans, for example. Also, we just published our first-- We have our first paper on the archive on mood. It's in a brain area called the insula, which is this amazing brain area. In the human neuroscience literature, if you look at where they're decoding mood from individuals who have electrodes implanted for epilepsy, the insula doesn't come up. The insula doesn't come up because you don't put electrodes in the insula when you're looking for epilepsy.

They just don't have the data. That's one of the components, I think, of that's one of the restrictions. When you're working in human neuroscience, you will be limited in ways that you're not as limited in animal research. I think the path forward for mood research is going to be human neuroscience. It's going to be animal neuroscience, and it's going to be comparative across human and animal neuroscience. It's going to be an all-hands-on-deck sort of situation in a way that you don't necessarily see even-- We should be doing this for all functions, but I think it's going to be even more essential.

Paul Middlebrooks
Yes, and that's right. One of the results from decoding brain activity is often like you could probably decode mood from recordings from hippocampal regions, but then you're not stimulating the insula. The lesson is that decoding is actually not that difficult when you have the right machine learning decoders working for you.

Nicole Rust
Absolutely. There's a difference between where a signal is reflected in the brain and the part of the brain you need to perturb to change that computation in the brain to change mood. Absolutely.

Paul Middlebrooks
However, I'm telling you, pretty cool technologies out there.

Nicole Rust
It is super, super cool. It's really inspiring what they're doing.

Paul Middlebrooks
I've buried the lead already. Your overarching conclusion, not conclusion, but push in the book is to develop what you call the grand plan. I want

you to describe that in a second, but the grand plan includes embracing things like complexity sciences, rethinking causality. I was tickled that you-- Tickled. I can't believe I just said tickled. I'm going to have to edit that out. I don't say tickled. I was pleasantly surprised because there are so many things that I saw that reflect my own journey that you devote a little bit of space in the book to shifting away from a things perspective to more of a process philosophy dynamical systems, for example, perspective. I want to talk about all those things, but what is the grand plan?

Nicole Rust
Before we jump in, I just want to say, because I think it's really important to say it, when I was writing this book, I didn't approach this book like Nicole Rust is the genius who's going to come sweep in and figure all this out. That's not what this book is.

Paul Middlebrooks
It just turned out that way.

Nicole Rust
No, no, that's not what this book is. I say that very explicitly in the opening to the book. For me, this book is really about curating what's happening in our fields, and from this really high level. Zooming in and just collecting all the bits of genius that our entire field has been talking about. Yes, the things that you're tapping into and excited about, that's really what-- I'm listening to your podcast. That's part of what's driving what's written in the book.

This really was a channeling the genius of the era. Yes, just zooming out, I think the grand plan of any era, this is how I'll define it, it's just this broad strokes description of how the community of research has-- It's an ethos that's driving ideas about how we're going to traverse from where we are to impacts to society. I think keeping the diversity of those impacts in mind is really important. We want to understand brains for all sorts of things. Understanding for understanding itself is an important goal.

Paul Middlebrooks
You still share that, right?

Nicole Rust
Absolutely. Yes.

Paul Middlebrooks
Because you do mention that in the book, but then I couldn't tell. It seemed like you've almost shifted completely to a treatment mindset.

Nicole Rust
I shaped the book around treatments because that's the one that seems to be the most frustrated. That's the one where people are pointing and saying, "This is not working." I could have written a book about neuro AI, but there's just all you can do is celebrate as you have on this podcast. It's just exploding. It's hard to keep up. You don't even want to write that book because it's going to be out of date in two months.

It's the field of treating brain and mental disorders where there seems to be a gap between what we're learning and actual, impactful treatments that can be deployed clinically. What is the grand plan? I think the grand plan doesn't make a lot of sense unless you rewind and think about the grand plan in the '90s and what went wrong, and then we can fast forward. In the '90s, researchers really-- we could talk about why, but they really began to rally around the idea of a brain as a very long system of causes that lead to effects.

Things like how the expression of a gene leads to a neurons function or how brain activity gives rise to behavior. That's what I mean. When you think about the brain that way, naturally you want to think about it's dysfunction as some sort of broken domino in that chain. You have this big domino chain, which is the broken domino, and then we can go in and target that broken domino for effects. If it's a gene, maybe that's a drug. If it's a brain area with aberrant activity, maybe we'll go in and stimulate it.

That was the find the broken domino and fix it era of brain research. That was effective for some disorders. We discovered postpartum depression after a woman gives birth. She has this hormone that plummets. If you can recover it, you can restore mood. It was effective in a lot of cases, but it turns out that there were other swaths of the field, which really just felt impenetrable to that type of approach. I would say the psychiatric conditions are among them. It's to this day, psychiatric conditions are still diagnosed exclusively based on symptoms.

Things like depression is diagnosed based on sadness and insomnia. There are no blood tests. There are no brain scans, not because that wasn't the agenda. The agenda of the 1990s was to develop those tests. Whatever it's going to be like, let's develop these biological tests for psychiatry, and it just hasn't worked out. Fortunately, I see the field shifting. I would say that's the old grand plan.

The field is shifting in this way, and it's just happening naturally. It's something you've talked about a lot on “Brain Inspired.” That is instead of just thinking about the brain as this feed-forward domino chain, embracing the idea that the brain is full of these big feedback loops. Now we have a system where causes are leading to effects, and those are feeding back on causes. That's a whole different type of system, and it can break in a whole different type of way. One of the things we know about these what are called complex dynamical systems is that their emergent properties can happen in surprising ways due to interactions between their parts.

They're not just about what their parts are doing in isolation. It's no longer a find-the-broken-domino type of situation, it can be calibration and interaction. The most profound insight, I think, that follows from thinking about the brain in this new way is how hard the end goal of treatments really is because we know that complex dynamical systems are exceedingly hard to control. The classic example is the weather. We cannot control the weather in anything but a trivial way. We can't dissipate hurricanes, not because we haven't tried.

There was a whole generation of researchers trying to control the weather, but it was really ultimately because we determined that it's all but incontrollable. The weather is a chaotic system. Small perturbations lead to these big unpredictable effects down the line. For me, thinking about that is the challenge that we're up against, we have to control a complex dynamical system. It just reframes all of research back to the earliest stages. As basic researchers, one of our jobs is to figure out where are the brain's control nodes.

Where are the places that we can actually go in and target a treatment that actually will shift the brain from an unhealthy to a healthy state? That's a whole different definition of the problem relative to find the broken domino and fix it. I would summarize it's something like-- It's definitely less pithy, for sure. It's something along the lines of model the brain as a complex dynamical system and figure out its control nodes, or figure out how to control it.

Again, for the benevolent purposes to shift it from unhealthy to healthy states. That I would say is the new grand plan of our era. That's what I'm going to stick my neck out and say in 30 years when we look back and say, what was the genius of our era? I think that's going to be it. We shifted to thinking about the brain as a complex dynamical system. We started thinking about how to control a dynamical system. That will be the game changer.

Paul Middlebrooks
I guess one thing to say here is that if you are in the domino way of thinking, fixing a single domino is a version of control, and it sounds like a very easy version. We do not know how to control complex adaptive systems. There are plenty of suggestions and maybe all of them have some merit, and maybe we can talk about some of those. One thing that you just mentioned that I wanted to ask you about also was you just said that like the weather or complex systems, I'm not sure if you just said this, but you talk in the book about how they are fragile in some sense, which made me--

Learning about complex systems, what you always hear or what I always heard is that they are robust because of all of the interactions, they can take on a lot of different configurations, they can adapt. You make the point in the book. I didn't appreciate it beforehand that yes, they are robust, but if you put them in regimes in which they have not evolved to be robust too, then all of a sudden, because they evolved to be robust in most regimes, they're actually fragile in a lot of edge cases. I don't know if I just explained that correctly, but maybe you could speak to that robustness versus fragility in--

Nicole Rust
Fragility. Yes. It's an observation about complex systems and I think it does have profound implications for the brain and brain disorders. Once you start thinking about brain disorders this way, you start to see, "Oh." It's like a light bulb moment. Like, "Oh, almost all the brain disorders follow from this." The general principle, the general idea is that because complex systems have these many interacting parts, they can become fragile if they have small failures or small uncalibrations.

The classic example is like an ecosystem, where if one of the species in an ecosystem gets a disease or dies for some way, you can get a complete ecosystem collapse because the entire ecosystem is so interdependent on one another. In the brain, these complex dynamical systems, that's the first thing you have to really appreciate is that they exist for adaptability. That can happen on different timescales. If I put you in a new country and a new culture, you'll slowly learn the language.

You'll adapt, your brain will adapt, your skills will adapt. That's a slower timescale. We can also talk about developmental timescales, even slower evolution. Then we have fast timescales. If you see a tiger, your entire body goes into a whole different mood, it triggers your fight or flight response, and then you run. That's a good thing. That's adaptability that you don't just exist in this one state, but you can trigger into these different states. That adaptability also tends to come with some fragility.

Going back to the see a tiger run, we know that if that system is triggered too often, you have chronic stress. It can burn out. You can mess up your day-night rhythm, so then you're messing up your sleep. You have insomnia, and sleep is when your body's repairing itself, that can trigger all sorts of downstream effects. It can also cause damage to structures like your hippocampus, which we know is really important for cognitive functions like memory.

It's adaptability, but it also has this fragility where it can burn out. Other classic examples of this when it comes to disorders, the immune system is just this beautiful orchestra of trying to find these little minute pathogens in the body. It's such a fine-tuned thing. When it gets a little bit out of whack, you can get a neuroimmune disorder. That's what multiple sclerosis is. It's a immune system attacking the myelin sheath of your neurons. There are other disorders like that as well.

Then there's the classic example of mood. Our moods are really shaped by our percepts of the things that happen to us, like good and bad. Good things happen, good mood; bad things happen, get in a bad mood. Mood is thought to exist as a running average of our well-being to motivate us. If bad things are happening, maybe you should do something different. You should go after the good things.

It's in this reciprocal loop where our moods impact the percept of the things that happen to us, which in turn impacts our moods. Here you have a system that it can spiral out of control, either down, or it can spiral up and turn into mania. There's a question, how does the system even remain calibrated given that it's so such a reciprocal system? There are all these examples all over. I think it's important to give these examples at so many levels to really get it, that this isn't just about mental disorders.

Another, this is not how maybe, the dynamical systems people would think about this, but this is how I think about it. In our brains have two ways to learn. There are ones that increase the strength of synapses and another one that decreases the strength of synapses. It can be Hebbian and anti-Hebbian learning. That second type, those two balance each other. If you want to have that second type, you have to have this whole host of mechanisms to support that second type. A mutation in one of the genes that supports that second type of learning leads to a syndrome called fragile X syndrome. That's a form of autism. By having more stuff, more stuff can go wrong. It's not a rocket science principle, but I think it's one with big implications.

Paul Middlebrooks
That one is one with fragile in the name actually. Those are heartbreaking that there are these-- I think Huntington's is another one that are so dependent on such a seemingly small change that can then affect the whole system. These are these important nodes of control, which is one way to control complex adaptive systems.

Nicole Rust
Absolutely. I just said, just to jump in there, I think that is like such an important principle as we think about rewinding to the 1990s. We have three disorders like that. You named them. Fragile X, Huntington's disease, and there's a rare form of Alzheimer's also, where if you have mutation in a gene, it leads to Alzheimer's with certainty. We've known about all three of these genes for over 30 years and we still can't cure any of these things.

Paul Middlebrooks
It's embarrassing, yeah.

Nicole Rust
Embarrassing, but also just makes you appreciate. This isn't about find a gene, make a mouse, create a drug type of situation. This is much more complicated. It's not that we haven't tried. There's a shift in perspective. I think that definitely needs to happen, and that researchers fortunately are making. Researchers in all of these fields are shifting to thinking about the brain in this complex way.

Paul Middlebrooks
You mentioned mood, and that's what you're interested in these days also. Is mood something that is affected by our modern lifestyle that maybe has not been-- that there's a cause, like a social societal cause, affecting mood more so than it has in the past because of our constantly being engaged on the internet and stuff, or have we just not appreciated it historically and we're appreciating it more? It was underdiagnosed or something, mood, pathologies disorders.

Nicole Rust
Yes. Certainly, that's a hard thing to tease apart, causes versus effects. That's also true of the autism field right now as well. We have many more autism diagnoses. Do we have more autism, or do we have just more diagnoses with the same fraction of the population?

Paul Middlebrooks
Same thing with ADHD, all these disorders that seem to have just exploded in the past decade or two.

Nicole Rust
Yes, what we can say, I'll throw out a statistic that's quite alarming, and it's one that is about the United States. That is the National Academy of Sciences, some years ago, did a report about deaths of despair, which can include many different things, but they include things like suicide and drug overdose. If you look at the United States and you just plot deaths of despair in many countries, Japan, Europe, Australia, Canada, it's flat as a function of time.

In the United States, it's increasing at an alarming rate. That suggests that there's something different happening in the United States. It's not about diagnosis, because these are deaths. It's not really even diagnosis about like what puts you in a category. We know it's not about the brains of Americans are different than the brains of Canadians, fundamentally.

Paul Middlebrooks
They seem to be, at least some of us.

Nicole Rust
[laughs] This is clearly a situation where environment is causing this. Then we could talk about what exactly in the environment is causing it, but I think it's incontrovertible evidence. That is also something that I've had to wrap my head around. When we think about what it even means to come up with an impactful understanding of mood, what do we even-- Where's our target? We know that mood is shaped by our brains, but also our experiences, and also our environments. By our experiences, I should say more our minds.

A lot of talk therapy, is an interaction between two minds, and thinking to yourself, to your own thoughts, and your own thoughts shaping your moods. We have brains, we have minds, we have environments. Each one of those can cause depression. Which one do we want to understand to interface with a treatment? Because you can interface at all levels. You could do a brain-based intervention, which might be a drug or brain stimulation.

You could do a-- that's cognitive behavioral therapy, which is really learning how to control your own mind, or you can change the environment of an individual. Alleviating all the factors that we know put them at high risk, like poverty and trauma, and that sort of thing. Which one of those should we push on? I think that that's a really important conversation to have. Yes, for me, I think it's an all-hands-on-deck sort of situation.

I will throw out there that I do-- when I think about what's the next big thing going to be, the next big breakthrough in understanding mood, I do think it's going to be in the brain because of those three, brain research is the one that's really moving at a rapid clip. We've been studying minds and interventions for a long time. We have a good sense of what trauma in the environment impacts mood. The big game changer, I think, is going to be in the brain. Not necessarily because it matters more than the others, but just because that's the era we live in.

Paul Middlebrooks
Even in the brain, what I want to ask you about is causality now, because you were just talking about different levels of causality and different facets. Even in the brain, maybe the way you used to think about it, the way that I used to think about it is that, okay, you just go and fix that little brain area, and then everything's going to be fine. That's the domino-like way of looking at it. Part of what you write-- In the book, you shifted from thinking whether something is causal, if it's causal, to thinking about how it's causal.

In the mood example that you just gave, you gave three or four different causal effectors that can shift your mood, top-down, bottom-up. That is one thing I appreciated in your book too, is you did the hard work of looking at different kinds of causality. What we want to say is causal and isn't, and that this is important if we want to understand how to control complex systems, is to understand that there are multiple causal factors going into a single thing, a single thing like mood, not that mood is a single thing. Maybe you could just speak to that, how your views on causality have shifted.

Nicole Rust
Yes, absolutely. There's so many things I didn't think much about before writing, sitting down to write this book, or the lead up to the book. One of them was causality. It's like, of course, we all know what cause means. We know what cause means.

Paul Middlebrooks
Billiard balls. Dominoes.

Nicole Rust
Exactly. That was a big wake-up call. It was a great example of a community-based conversation in terms of how we arrived at the conclusions that I'm about to tell you. It was a realization that when brain researchers use that word cause, they are often talking about it in different ways. Those ways can loosely map onto the domino chain way of thinking versus the more complex systems type of thinking.

I think a good example of this is reading, and what has to happen in the brain to cause us to read. In the first way to think about causality, it's called causal production. The goal is to figure out the causes that produce things. We would focus on things like the visual word form area, which transforms shapes into letters and words. We would say that is causing reading in a way that the eye is not. The eye is necessary for reading, but it doesn't because reading because it doesn't because reading in any way--

It causes seeing, but reading is a special type of seeing. The spirit behind this type of approach is the idea that if someone has reading deficits, but not seeing deficits, so ones that don't trivially follow just from seeing, then that's probably where we want to target. We have to figure out the causes that produce things in the brain. Which of the domino chain in the domino chain is actually the right one. That's one way of thinking about causality.

Paul Middlebrooks
Causal production.

Nicole Rust
Yes, causal production. Like you said, causality can actually be really complicated. It can happen at different levels. In a complex system, you're not going to have a single cause that necessarily produces things. There's this broader way of thinking about causality where you zoom out, and that is called causal dependence. It's the idea that anything that has an influence, not just by correlation, but due to the counterfactual, like if X did not happen, Y would not have either.

If you don't have eyes, you can't read. That's the bar for causality. In that depiction, the eye is causal for reading. That's great. Now we have this bigger sense of causality. It's important because therapeutic interventions might not target necessarily the-- even if you have a causal production system, you might not necessarily target just that domino. One example is a blood pressure medication. If you have high blood pressure, your doctor might give you a medication that changes the diameter of your blood vessels, even if that wasn't the problem in the first place, because it just recalibrates the system in order to lower blood pressure.

It's a recalibration type mechanism. Causal dependence is important for finding those therapeutic targets. At the same time, it also leads to, and this took me a long time to scratching my head, then what is my job as a basic researcher? I'm just supposed to go through, and I'm supposed to document all the causes. Even in the reading case, reading is disrupted when a bee stings you. Also, if there's a hurricane, and also if there's a tornado.

Am I really supposed to exhaustively document all of the things that influence reading? That seems a little bit like a waste of time. That can't be right. Yes, the big realization for me is what you said. We're not here to create lengthy yes, no checklists about what causes something and what doesn't. We're here to build models. We have a phenomenon of interest, and we want to build how these different causal influences interact in order to create the phenomena of interest.

One of those things would be the visual word form area. One of those things would be the eye. We would talk in those models, they would include the different roles that those two things play. Then, of course, there would be a big bucket for you also have to be free of disruption. All of those things would contribute to a good model of what in the brain causes reading. It's definitely a different way to think about it, the agenda, but for me, it was so clarifying, like what is my job here?

Paul Middlebrooks
Yes, you lament in the book, saying the answer, I'm sorry to say, because it's going to be hard, is that basically we need to model everything. You just said we're not going to have an exhaustive checklist, yes or no, whether something is causally productive and dependent, and of all the facets. By the way, I can't wait for bee sting therapy to be a thing. Any model is necessarily an abstraction of something. Of course, you quote George P. Box, “all models are wrong, some are useful,” and others of his quotes in the book. Knowing which of those locuses of importance, causally, is something that has to go into the model then, otherwise we're missing facets of it. That seems like a tall order in a complex system, which has multiple levels of interacting different processes that it seems-- All you can do is start to model it and then see where it's working, where it's not, I suppose.

Nicole Rust
Yes, I think there are two routes in, and one is the route that-- Let me just emphasize. This is an all hands on deck situation. People are suffering and they need treatments. We have a long history in brain research of just intuiting what might work and giving that a try, even in the absence of complete understanding. We still don't know how most of the therapies to treat brain disorders actually work. That's completely fine. There's no, "You have to go through this long process and we have to hold off and wait."

There is one route in that's of that type, and then there's another route in like you've described, and that is model the system and all of its complexity. For that example, I turn to this really elaborate description of the genetic network that controls cell death in a form of cancer leukemia. This big genetic network has, I think, 60 different genes and proteins, and everybody's interacting with everybody else. It's really, really complicated.

Researchers went in and they modeled all those interactions. Then, once they had them, this big complex, dynamical systems model of those interactions, they were able to ask the following question, what in this model actually matters for determining whether cell death is on or off? A lot of stuff in there is doing a lot of other stuff other than that question. What they have is a situation where cell death has been turned off and they want a therapeutic way to turn it back on again.

They got rid of all of the proteins in that network, except for five. There were three that were configured in this domino chain backbone, and then there were these two controller proteins that were determining whether or not the backbone was on or off in order to control apoptosis. That whole process is a process, it's derived from engineering. It's called model reduction, and that's definitely one way into the system.

You can imagine that this is going to be really important. It's already being deployed for things like Parkinson's. I imagine it's happening for Alzheimer's too. That's one way. There's another way, and I think that we definitely want to pay attention to that one too. That is, we can either intuit what control nodes might be. Here I would point to the arousal system in the brain as an obvious control node. The arousal system exists to wake the brain up.

When something important happens, it involves a neuromodulator norepinephrine. That's an obvious control node. We can just say, well, obviously we can interface with that one. There might be some cases where we also just throw up our hands and say, "This might be uncontrollable in a brain-based therapeutic way." That's where the mood disorders come in certain cases. It might be that some classes of depression are just a brain that has gotten entrenched in a maladaptive state because it's just learned its way in there. The only therapy that's going to fix this is a benevolent reprogramming of the brain.

Paul Middlebrooks
LSD?

Nicole Rust
That can't happen via-- [chuckles] That's where we get to LSD because we're never going to be able to go in and give some holographic optogenetic therapy that's going to tweak all the synapses in exactly the way they need to in order to get the brain out of that state. Acknowledging, like that is not the goal there to try to do that. What we can do and this is where the psychedelic therapies are starting to gain some traction, the idea behind those is you just want to trigger plasticity in the brain.

You want to enhance plasticity and you want to combine that with talk therapy because talk therapy is the only way you're going to be able to reshape the brain in the way it needs to. You're not going to be able to do that in an interventionist way in the brain itself. There's evidence that so many of our therapies for depression, that's how they work. They're really enhancing plasticity so the brain can like wiggle itself back to health, which is I think an important insight. It really informs how we should be going about it, if true.

Paul Middlebrooks
Yes. The psychedelics research. A dynamical systems landscape way to look at this, and I'm just restating what you said, is that, you have these attractor states wells in this landscape and you might get stuck in one. The way that I think of psychedelic treatments, I'm sure that I just read this, I didn't like come up with it. It's just a resetting of that landscape, a flattening out so that then you can get to a better place with the talk therapy, et cetera, and then, slowly over time, go back into a better well, a better attractor state in that landscape.

People who have these psychedelic treatments, sometimes it's just one shot and it's very effective. It does seem that while fun, that might not be the best treatment. In 50 years we might look at like psychedelic treatment and think, "Man, we've just shocking the hell out of the brain. That was like really unnecessary, and there are better treatments now." I don't know how you think. It seems a little scary to think I am flattening out my entire landscape to get to a better spot in this one [chuckles] well. I don't know how you think about that.

Nicole Rust
Yes. I think we only want to do something as dramatic as is required.

Paul Middlebrooks
Sure.

Nicole Rust
Yes, electroconvulsive therapy is a very dramatic resetting of the brain. Having it enter a seizure. There are ideas that that's how that works as well. You want to do the minimally invasive thing in order to enhance the plasticity that you need. I think we also have to acknowledge just the dangers and the risks. When you flatten the landscape, it can land anywhere. These talk therapies where a patient is reliving their trauma, that can just reinforce the trauma and actually make it worse, not better. It's really important that we proceed cautiously and ethically. People shouldn't be messing around with this stuff based on something they Googled or something.

Paul Middlebrooks
Right.

Nicole Rust
This is really, really tricky stuff, yes, that needs to happen in a professional setting.

Paul Middlebrooks
Yes, I was just having a conversation.

Nicole Rust
We need a lot more research.

Paul Middlebrooks
A lot more research.

Nicole Rust
A lot more research.

Paul Middlebrooks
Fortunately, people, recreationally, do these things as well, so that that could be [chuckles] some sort of research. I have a friend who just partook with some, I think it was shrooms, and he wanted to talk about his experience. I said, "Oh, did you meet God?" Kind of jokingly. He said, "I think I met the devil." [chuckles] There's like lots of different ways it can go.

Nicole Rust
That could be traumatic. Yes.

Paul Middlebrooks
He's fine, though. He's fine, I think.

Nicole Rust
I'm glad. He's fine. Be careful out there.

Paul Middlebrooks
Yes. You discuss in the book that the work of Hasok Chang documenting how we came to measure temperature through something he eventually calls epistemic iteration, that it was a long back and forth. You write in the book that this gives you a little bit of hope in this daunting challenge that you put forward of building models of everything and understanding complex systems.

This is from the book, *Inventing Temperature,* by Hasok Chang. I can say John Krakauer recommended this book to me many years ago. I think everyone who's read it has had some sort of epiphany and just really appreciated this historically about whatever they're doing that's daunting. We'll look at this example from history. How did it affect you? How did Hasok Chang's work affect you?

Nicole Rust
Yes. Thank you for that and asking the question. I talk about *Inventing Temperature* like twice a week.

Paul Middlebrooks
Do you really? Yes.

Nicole Rust
I'm always like, yes, to individuals. I'm always struck by how many people haven't heard of it and haven't got the memo. It's also--

Paul Middlebrooks
Let me just say it's a philosophy book that is very readable. I had the chance to see Hasok give a talk at the University of Pittsburgh a few weeks ago and it was really pleasant as well. I just wanted to--

Nicole Rust
Yes. Yes. Oh. I have never seen him speak. That would be delightful. I'll just put that in context for me. When I was writing this book, I realized that I had-- again, one of these things like you just don't think about stuff until you think about stuff. I had internalized this idea about progress in science, where one generation locks down a bunch of answers and then the next generation builds on those answers. That's how science progresses.

Paul Middlebrooks
Shoulders of giants.

Nicole Rust
Yes. I was finding myself getting a little bit pessimistic because I was having a hard time finding evidence of that in our field. It felt like we were just circling around the same questions again and again. It's not like we were figuring out V1 and then moving on to V2. [chuckles] We're just sitting there in V1. I was like, what's going on here? Yes, Chang gave me a new insight in scientific progress that made me feel much more optimistic.

The idea is not lock down and move on, the idea is iterate and refine and improve. He really takes on, yes, just this classic question. Step back and think about, you're trying to figure out how something works. It might be temperature, or it might be today, mood. You have to start with some type of measurement of it. Of course, once you figured out how it works, you will know how to measure it, but you need measurements to create understanding, and you need understanding to create measurements. Where do you begin? Chang argues that it's okay to jump in with just a best guess. It's not going to be right, but you can just jump in and it will be close enough that if you're committed to refining over time that measurement, you'll get there through iteration. That's the key. He examines, yes, how did we figure out temperature in the 16th century? How did we go from the sense of what hot and cold are to the observation that puddles freeze, to developing the first thermometers?

Then, over a period of 250 years, create thermodynamics and statistical mechanics and be able to measure, temperature within a billionth of a degree of absolute zero. That's what we want for depression. We want to go from where we are today, which is a sense of what depression is. Some of these rudimentary questionnaires like, "Are you sad? Have you slept?" We want to go to like the thermodynamics of depression. That's what we want, in addition, be able to intervene and change it.

That's epistemic iteration. I think it's just such a powerful concept because it is so illuminating. One of the things Chang emphasizes is it's not a prescription. He examines the history of, temperature and he says, "Well, it began with getting a really good thermometer before that thermometer had any impact on the theories." It wasn't that the theories weren't created in parallel, but the measurements didn't have any impact on the theories until we got really, really good measurements.

In the book, I go into examples from memory where it looks like it was done a little bit differently. The theories about memory were intertwined with our measurements of memory because it's just a different type of thing. It's just really, for me, illuminates the formidable challenge we're up against. It makes me feel, "All right," as I go in and try to study mood. I don't have to come up with the ultimate measure of mood in order to make progress in mood research. I just have to come up with something that's decent and be committed to iterating.

That's why I think depression is really interesting as well. It turns out that the measure of depression that's used in most clinical trials today for antidepressant drugs, that was a scale that was developed in the 1960s. As Eiko Fried and [chuckles] his colleagues say, "since that scale was developed, we have put a man on the moon". We have created computers. They're in our pockets. We're connected globally and we're still using the scale from the 1960s. Maybe it's time to iterate at the same time.

If you just zoom out and you look, it turns out that there are 250 scales like that. I would like to chime in with my own two cents and say, "I don't think the next big step in depression research is going to be the 251st scale for depression." I don't think that's going to be the big breakthrough. We need a new way to measure mood and depression. That's going to be the big breakthrough, I think. Iterating, measuring things in different ways. Yes, but I think we have to think about it like that.

Paul Middlebrooks
A couple things to add. One, and you mentioned this in your book also is that, Chang points out that epistemic iteration never ends. There's never an end because you're always iterating. [chuckles] You said it's not prescriptive. Mood is a different beast than temperature. In one sense, like it's hopeful in that you see, "Okay. This was a hard problem, but through this epistemic iteration, we got to where we can measure temperature very well."

However, it seems also like a much simpler problem than brains, then complex, because temperature, it's a statistical property but it is just sticking a thermometer in and measuring. What you put in that thermometer, it makes a difference. Whatever elevation you measure at, how many minerals are in the water, all of these things, which Chang goes through the pains of like talking about, and that took, as you said, 250 years, I think. [chuckles] The other thing is the brain is different and also we don't want it to take 250 years. Right?

Nicole Rust
Yes.

Paul Middlebrooks
I don't remember if he pointed out-- Well, I guess my question is like, do we have a better science of effective iteration to speed things up? Do we know a better way to go about iterating?

Nicole Rust
I would say, we don't know definitively. One of the lessons that Chang points to in his book is the importance of standardization in measurement. There was this period, where everyone had the thermometer, but they couldn't agree on a temperature scale. Like you said, they couldn't agree. Everybody was doing something a little bit different in order to have a community-based science of measuring temperature. It helps if you all have the same thermometer measured in the same way, so you can really compare your results.

Yes, there was a committee formed and they agreed we're going to measure it in this type of vessel with this, and the benchmarks are going to be water freezing and boiling, and so on, and so on. In the case of depression research, that committee met in 2019 to agree with a scale for depression that all researchers should use in order to measure depression. At least all of the studies of depression will, have at least one measure that's in common.

It only makes sense to do some standardization now in this era of big data. If we want to piece together things, we have this incredible new tool, machine learning and artificial intelligence that can help us navigate through all of this, but it helps a lot if it's not apples and oranges. There's at least one apple that can tie all of the different things together. I would say that's one principles, some standardization, but standardization is also at odds with iteration.

That's really what's been the spirit of what's been keeping this measure from the 1960s alive is we can compare the clinical trial outcomes today with a clinical trial that happened in 1972 because we still have this one scale. I think we have to be very thoughtful about the trade-off between, "Yes, we want standardization, but, yes, we also want iteration. How are we going to achieve those two goals?" That's a harder question to answer.

Paul Middlebrooks
It is. I know that you're aware of the adversarial collaboration in consciousness studies designed to, for the different advocates of various consciousness theories to agree on some experimental paradigm, which is like a standardization that will come up with numbers. Then they have to make different hypotheses of whether it supports or whether it falsifies the various theories. Even attempts to do that, like some of the theories drop out because they say, "Well, it's not even a valid question because my consciousness theory isn't amenable to like these measurements. A measurement like that would not say anything, pro or con theory."

In some sense it's awesome because it's getting adversaries to agree on some standardization to make progress. On the other hand, it's just as frustrating because it doesn't fully falsify any theories. We still don't understand consciousness anyway, what it is, but it's subjective, and mood is somewhat like that. Can we standardize something like mood better than something like consciousness?

Nicole Rust
It's a really important question. Yes. There's this tension here. Maybe two thoughts. One, this is the same tension between like little team science and big team science. When is the field ready to put all their eggs in one big experimental basket versus when is a field, better off by doing a whole bunch of different things? I think that when a field is ready to put all their eggs in a big basket, that's when you're ready for an adversarial collaboration, and that they can happen too early.

I would say in the case of depression research, I don't know a big competing theories that would justify something like an adversarial collaboration. I came out of writing this book, a huge fan of-- A specific form of pluralism is that is acknowledging that we don't know what's going to work. What we want to do, it's not that we want to just say anything goes no matter how silly it is, but we do want to just acknowledge some epistemic humility.

You don't have to think that your way is the only way in order to have an intuition that, "I think this is the best way, but let me acknowledge that other way, that might be actually very useful too." Kind of, "We're in all hands on deck, so let me try to understand what you're doing and why you're doing it. Let me acknowledge that we need to pursue multiple paths."

It might be that only one works or one ends up to be the best, but we don't know which one is going to be that. I think that's one. That's probably where the mood and depression field are, kind of an all hands on deck. We need lots of things happening in parallel, but we also need lots of conversation and discussion around it. Then, yes, there are more advanced fields where you're--

Paul Middlebrooks
Consciousness is not one of those more advanced fields.

Nicole Rust
Yes, I don't want to chime in on that because I just don't know enough about to know, but I can imagine it's a little too early consciousness. They're doing wonderful things in this and the models of the visual system. The whole Brain-Score enterprise. That's a wonderful example of we want to model the visual system and we want to agree what the benchmarks are and what the targets are, so we can compare the models against one another. That's just a big community-wide conversation. What is it that we're trying to explain in the first place? Because that's going to determine the models that are the best and they're ready for it. Yes.

Paul Middlebrooks
All right. We don't have too much time remaining. There are a few other topics that I wanted to get to. Okay. We talked about the grand plan, but another phrase that you use is perspective neuroscience, and you write about how this, exercise of writing the book, is what you consider, perspective neuroscience, which is this zooming out essentially.

I'm reframing.

I've heard this for about 10 years now, that what neuroscience needs is to zoom out and think about big pictures and reconfigure. I don't know that it's happening more or less. It seems to be happening more with people writing books like this, and you allude to perspectives in research journals, which is where perspective neuroscience I think gets its name. do that. Did I describe it correctly? What would you add to the idea of perspective neuroscience?

Nicole Rust
Yes. Perspective neuroscience, it's been fun to talk to you about this idea and I'm excited about the work that we're doing together in this space because I think we're both really interested in perspective neuroscience. Talking, about what it is and what it isn't right, and how to think about it, I think is really, really important to hash that out by like-minded individuals who are deeply engaged in it.

To me, yes, I think about perspective neuroscience is that big picture conversation, about how, for example, all the ask answer pieces of the puzzle fit together. It is not exactly philosophy, because I think, philosophy, if you just look at the topics of philosophy, they're not always relevant or of use to practicing scientists. Some of them are. It also has history. It's an appreciation of what has worked in the past, like this conversation about Hasok Chang and inventing temperature. It ties together so many things.

I think it's important to acknowledge that the goal of perspective neuroscience is not prescriptive. It's not this idea that, "Okay. We're all going to sign up for one grand plan for our era." That the point of perspective neuroscience is really just to put forward a series of ideas about what we should be doing, and how we should be doing it, and why those are good ideas so we can discuss them.

Then, we also do need to appreciate, pluralism to the degree to which we have to be humble about the fact that we don't know what's going to work and what isn't. Let's agree that multiple paths forward are important. I think there are mixed feelings about this type of discussions. Some people will acknowledge out loud, "Oh, this is just a waste of time." Somebody wrote too many perspective pieces and they didn't do enough science.

Paul Middlebrooks
Shut up and calculate.

Nicole Rust
Yes, exactly. I can appreciate that the end of the day, science is about the really, really, really hard work. About doing asks and answers and traversing all the experiments and all the analyses, unquestionably, if that doesn't happen, scientific progress doesn't happen. At the same time, given how hard science is, I think it makes a lot of sense to think really hard about what we're doing and why we're doing it. If you're going to engage in this, why not do science that really is going to move the needle of science that's going to matter? Trying to even understand what that is.

We don't just want to get caught up in inertia of the history of our fields. We want to be thoughtful and say like, "Well, what is it that we're trying to achieve?" That could be all sorts of things. I want to understand, I want to build AI, I want to treat brain dysfunction, whatever it is. Specifying the goal and then working backward and saying, "What is the most important thing I could do to contribute to that goal? Am I doing it in the most sensible way?" I think that that's perspective neuroscience to me is having that conversation. I think we should be doing more of it, for sure,

especially at the trainee level. Trainees are not encouraged to engage, and I don't think we're doing enough to help them engage in perspective neuroscience.

Paul Middlebrooks
Yes. Students have a lot on their plates already. This sort of perspective taking, for instance, it took you years. It's taken me years, and I'm constantly learning and shifting my own perspective, and appreciating pluralism, and practice, and learning whole new fields, and it just takes a lot of time. Would it be at the expense of other things that are considered important right now that are maybe less important? What is the right training regime?

Nicole Rust
What is the right training regime on these things? Yes. I don't know the answer to that. I don't think it should happen right, too extreme. We can't all just sit around and think, and read books, and hang out on social media all day.

Paul Middlebrooks
Right. It's important. You constantly hear it's important. Right.

Nicole Rust
It is important. I'll point to something I just really appreciated. That was the first talk I gave in this space was at the Cognitive Computational Neuroscience meeting last year. I had so many trainees come up and just say thank you.

Paul Middlebrooks
Oh.

Nicole Rust
I have had a hard time myself putting the pieces together and just for you to open this conversation. I'm so appreciative. You can imagine that a meeting like cognitive computational neuroscience every year, how about all science talks and then one talk that's on perspective neuroscience. That seems that-- What is it? 15 to 1 ratio or whatever it is, that seems worth investing.

Maybe that is a good investment where we're going to get more out of that one perspective neuroscience talk than we would if we just had one more science talk in the queue. I think we're not devoting enough resources to it. I do want to address the second part of your question, which I think is an important conversation. That is, how can you be both intellectually honest, humble, but also not take down the entire field.

Paul Middlebrooks
Oh, right. Yes. I keep having this little story circling in my head a couple of years ago, a cousin-in-law asked me like, "What do we know about the brain?" I was like, "Basically nothing." I felt like I just stabbed myself in the heart, because it's not true but there's so much that we don't know.

Nicole Rust
Yes. It's easy to just get like, "Where are you?" At any one day. Like, "Are you in the downer cycle or upper cycle?" I do think that as researchers, we do have a responsibility to give not the most pessimistic version of ourselves when we show up, because I don't think it's the most accurate version of what happens in the field. I thought about that a lot when I was writing the book. There are a lot of takedowns in books, especially in the psychiatric space. We haven't done anything. We haven't gone anywhere. We don't need another book like that. It's a horrible and tragic history in some of those cases.

Paul Middlebrooks
The takedowns are always easier than constructive.

Nicole Rust
Exactly. I think that that's my take home message is, I told myself, "This can be a personal journey for me that I go on, but if I'm going to show up to society and actually write this down and spread it with everyone else, I'm going to bring it to that constructive place," or, "I just won't write it. I'll just shut up. You don't have to hear from me." For me that book was so transformative, because it very, authentically, that path was one for me from pessimism to just unequivocal optimism about the future of our field.

I could say that very honestly with a straight face, like, "I'm all in. Let's go. I can tell you why the brain's so complicated. I can tell you what we're going to do about it." That journey was empowering for me. I think that that's the last thing I'd want to say about this public-facing communication is, I think scientists underappreciate how much it can give back to you by having to zoom out and talk about things at these really high levels, you see things you've never seen before. You get excited about things that you--

The puzzle get put together that you didn't realize. That's a huge benefit that I think not everyone realizes. It's not just about service or obligation. This is really about even enriching your own intellectual experience. Yes, putting that emphasis on, you got to take it to somewhere constructive. You can't just be destructive if you're going to have this in these public venues. That does not mean that we have to do things, like say, "Scientific fraud, doesn't matter because, oh, it's such a fract--" No scientific fraud matters, we come down-

Paul Middlebrooks
Oh my God.

Nicole Rust
-but we say, "Okay. Here's what I'm going to do about it. I'm going to participate reviewing this many of the papers flagged on PubPeer, or whatever." There are many forms of constructive, that's the thing I want to emphasize.

Paul Middlebrooks
Yes. People have different skills and interests, and so maybe not everyone needs to do perspective neuroscience, for example, or advocacy because people have different interests and skills. I'm glad to hear that you're now-- Modern Nicole Rust is the optimistic, delusional Nicole. No, I'm just--

Nicole Rust
She totally is. She's totally. Yes, she's at a high. [laughs]

Paul Middlebrooks
That's great though. It's great that-

Nicole Rust
Absolutely.

Paul Middlebrooks
-you're at a high. I wanted to ask you about philosophy. I gave my little take and you do, you write about like process-based perspectives versus things perspective. You've already mentioned today how some philosophy is more useful than others, but how much of the zooming out, how much were you affected by philosophical counts of the ontological status of things? Did it just shape your perspective? How did it affect you? The philosophical approach?

Nicole Rust
Yes. It's a really good question. How do we get our influences? I don't read actual philosophy journals- [crosstalk]

Paul Middlebrooks
Why would anyone?

Nicole Rust
-or books. I don't feel that informs or influences me in ways that I can really connect with. That's not a criticism of their field. They don't exist to help Nicole Rust with her science, and I don't do my science to help them with their philosophy. That's okay. I get these insights through a filter and I deeply appreciate those individuals who are helping with that transition and that filter. I would point to, for example, Lauren Ross at UC Irvine is someone who she's terrific about swooping in and looking at brain research and saying, "You know."

One example of that would be a paper she published recently with Dani Bassett, where they noted that there's a gatekeeping or a criterion for papers to be published in certain journals or grants to be funded by certain agencies that the criterion is mechanism. It has to inform mechanism. Lauren said, "Look, at all the ways you're using this term mechanism, you don't really agree with what that means."

Paul Middlebrooks
It's still mechanistic-

Nicole Rust
Yes.

Paul Middlebrooks
-in your abstract.

Nicole Rust
Exactly. Isn't that a problem when you're gatekeeping with something that you haven't even defined yet? What I really appreciate about Lauren is she doesn't come in and say, "Therefore, this is how you should define mechanism." She just says, "Look, these are the ways you define it. Some of them are connected to causality. Some aren't straight. Let me help you wrap your heads around it. You as a community need to figure out what to do with this information. It's not my job to, because that's not my role here. I'm not a brain researcher.

Paul Middlebrooks
However, where is that in the spectrum of takedown versus constructive? Because it's somewhat-- [chuckles]

Nicole Rust
I find it's really constructive in so far as it's illuminating. It's not just journalistic reporting in that, like, "Oh, these are the things that happened and

they were horrible." It's takes it beyond. It's like conceptual organization of the field. I would say it's constructive in that sense. Yes, so those individuals, I really, really appreciate interfacing with at the, at the interface of philosophy and brain research.

I think that that's really important. Just having feeling also emboldened to own our words and, we need to define what we're talking about, but we don't need to feel constrained by-- There's like a whole big talks about like the philosophers use representation in a way that's very foreign to us, and they have a good reason for it.

Paul Middlebrooks
I'm just about to have like five people on who are in these representation debates. I'm worried, how do I do this where it's not just a philosophical black hole?

Nicole Rust
I think part of it is also just feeling, yes, emboldened to own what we mean and define it. I think that there's a lot of clarity that comes like the word cause, and that can be insightful, but we have good intuitions for-- [crosstalk]

Paul Middlebrooks
I'm with you. I really appreciate that handful of philosophers of science who helped translate. Because an example, on the other side where you can get lost is, William Wimsatt. Bill Wimsatt is a philosopher.

Nicole Rust
Yes. I have his book.

Paul Middlebrooks
Is it *Re-Engineering Philosophy For Mortals* or something?

Nicole Rust
Yes. Yes. Absolutely. Great cover.

Paul Middlebrooks
Oh, yes. It's got a great cover, and it's got great concepts. Wimsatt talks about the causal thicket, which speaks to what we were talking earlier about with causality that in this mesoscopic spatial world scale that we live in, where things can matter across levels, across spatial and temporal levels. He calls this the causal thicket where it's not if, but how things, various things are causing each other. He's got a great illustration. I tried to read the book and it was so difficult for me to read that I just put it down and I felt a little sad about that. On the other hand, it's not a constructive use of my time, I don't think, if I have someone who can translate the concepts to me because I am mortal.

Nicole Rust
That's my experience as well. It's just like, "This matters to someone, but I don't see how it's going to move the needle on understanding my ability to understand like what in a brain drives mood?" I need to move along.

Paul Middlebrooks
Yes. Someone who just helps us grasp, "Okay. What's the important stuff from this that will affect my thinking and my own research?" Nothing against Bill Wimsatt. I still might invite him on the podcast, but anyway. Okay.

Nicole Rust
Yes. Yes.

Paul Middlebrooks
Last question for you here, unless-- First of all, did we miss anything that you wanted to highlight before? Okay.

Nicole Rust
I don't think so. Yes, we've covered a lot of territories.

Paul Middlebrooks
We've covered a lot of territory and not nearly as much as your book covers, [chuckles] I guarantee you. I mentioned consciousness earlier. You're interested in mood these days among other things, and that's a subjective thing. You mentioned the Crick book and part of your excitement was, "Well, we will be able to make progress on understanding subjective experience for lack of--"

That's a high level summary. Has your shift, the many shifts that you've gone through in your new collection of perspectives, has it changed the way that you think of what consciousness or subjective experience is? Has that complex systems approach the dynamical systems approach? I asked because I still can't articulate for myself, which is a problem. I can't write a book, how I--

My thinking about consciousness and subjective experience has changed how it might arise the nature of it, but I'm at a loss to really write a clear paragraph about it. Part of my shift has been, like you, appreciating complex systems, appreciating dynamical systems, and so on. Has it changed the way that you think about consciousness at all? [chuckles] Have you just left that alone because mood is hard enough?

Nicole Rust
Certainly, mood as a subjective experience, is all tied up there in consciousness. I'm still wrestling with those ideas. There's an idea in the field that an emotion is a brain state and a feeling is a conscious experience, right. That's how we distinguish them. That's one argument and others argue that's not true. So much of that debate shapes the entire field. It informs like, "Can we even study emotion in animals? Do they actually have feelings? What would that mean? How would we know?"

As I make this transition, to studying mood, all of those questions are really at the front. I think those questions are so easy to get lost in if we don't keep our eye on the prize. That is people out there are suffering. They are suffering from depression. It's about 20% of individuals will experience a mood disorder at some point. For half of the individuals who try antidepressants, they don't work. Certainly we can't help everybody that has depression, and so we have to jump in and try some stuff.

I think we can argue about, some of these things, but at the end of the day, it's like, "Well, this might work, so let's give it a try," in terms of understanding the neuroscience of mood in an animal. "Let's give that a try and see if that works." In terms of how my thinking has changed, definitely-- It's an easy sell these days. The idea that consciousness is an emergent property of a complex dynamical system. I don't think anyone's going to say, "Oh, no, no, no." It's about that special neuron, it's the von Economo neurons in the insula when they fire, they've got the special magic protein. That makes us conscious. Nobody thinks that way anymore.

Paul Middlebrooks
Nanotubules, right. There are some people-- Okay. Yes.

Nicole Rust
Maybe. Maybe. Even efforts to measure consciousness are all based on these dynamical systems. It makes me realize, yes, just the sheer awe of what we're up against seems like it's more respectful of the problem. This is this emergent property-- Thinking about not just the brain gives rise to, but we are agents that interact with our environments. We shape our environments, our environments shape us. We are a dynamical system in that sense as well. Also seems to respect some of the awe and wonder of the things that we are. We're not brains in a vat as far as we know. Yes.

Paul Middlebrooks
I'm glad you said that because I have that same shift. I can articulate that. I think I would 10, 15 years ago would have said, "I want to understand how the brain gives rise to." I might still say it and slip up and say it but that's not how I think about it anymore. All right. That removes something, but then how can I be constructive and say something positive? Is what I struggle with.

Nicole Rust
Yes, absolutely. I was very moved by Kevin Mitchell's book, *Free Agents*-

Paul Middlebrooks
Yes. You are right on that as well.

Nicole Rust
-where he brings back, how could free will exist in a world that is deterministic or largely deterministic. Thinking about from a dynamical systems perspective of there are these top-down mental states that maybe are imposing upon, neurons and their function, and there is some noise in there. Yes. I guess I would just reiterate, it feels like we're on a course that's more respectable of the awesomeness, more respective of the awesomeness of what we are somehow.

I don't think that we're going to figure this out by taking all that on. I think we're going to figure it out in small slices. We have to work up to some of these big, awesome questions scientifically. At least that's my inclination as a scientist. I'm not going to try to go explain all of the awe and wonder of the human condition. That's not something that I could productively do, but I can go figure out, what drives the neuroscience of mood. I'll start there.

Paul Middlebrooks
With your many models, epistemic iteration approach.

Nicole Rust
Exactly.

Paul Middlebrooks
Okay. Nicole, thank you. I'm really happy that you're so optimistic. I wonder, if that's a normal pattern. We all start off, really optimistic, and then we learn some things, and then we think, "Oh, no." Then, maybe we get a grant or something, and then you get a little optimistic. Right now you're on a high, and that's great to see. It resulted in this book. Maybe the book resulted in your optimism, or maybe they epistemically iterated with each other. Thank you for the book. I recommend it. I hope it does really well. Thanks for joining me.

Nicole Rust
Thanks so much, Paul. This has been a ton of fun. I really, really appreciate it. 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 advance research. Visit the transmitter.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]
